10/626173

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=> d his

     (FILE 'HOME' ENTERED AT 13:55:08 ON 13 APR 2005)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 13:55:36 ON 13 APR 2005
L1             17 S "CARK"
L2           1949 S "CARDIAC-RELATED"
L3           4025 S ANKYRIN(2W)REPEAT
L4              4 S L2 AND L3
L5              3 DUP REM L4 (1 DUPLICATE REMOVED)
L6             15 DUP REM L1 (2 DUPLICATES REMOVED)
L7       11583440 S MODULATOR? OR INHIBIT? OR ACTIVAT? OR STIMULAT?
L8           4037 S CARDIAC (2W) RELATED
L9              4 S L8 AND ANKYRIN
L10          2200 S L3 AND L7
L11          1035 S HUMAN AND L10
L12            87 S CARDIAC AND L11
L13            40 DUP REM L12 (47 DUPLICATES REMOVED)
                  E RAJU J/AU
L14           111 S E3
L15             0 S L13 AND L14
L16             2 S (L2 OR L3 OR L1) AND L14

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                  (ROSPATENT) added to list of core patent offices covered
 NEWS  4  FEB 28  PATDPAFULL - New display fields provide for legal status
                  data from INPADOC
 NEWS  5  FEB 28  BABS - Current-awareness alerts (SDIs) available
 NEWS  6  FEB 28  MEDLINE/LMEDLINE reloaded
 NEWS  7  MAR 02  GBFULL: New full-text patent database on STN
 NEWS  8  MAR 03  REGISTRY/ZREGISTRY - Sequence annotations enhanced
 NEWS  9  MAR 03  MEDLINE file segment of TOXCENTER reloaded
 NEWS 10  MAR 22  KOREAPAT now updated monthly; patent information enhanced
 NEWS 11  MAR 22  Original IDE display format returns to REGISTRY/ZREGISTRY
 NEWS 12  MAR 22  PATDPASPC - New patent database available
 NEWS 13  MAR 22  REGISTRY/ZREGISTRY enhanced with experimental property tags
 NEWS 14  APR 04  EPFULL enhanced with additional patent information and new
                  fields
 NEWS 15  APR 04  EMBASE - Database reloaded and enhanced

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               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 10 JANUARY 2005

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FILE 'LIFESCI' ENTERED AT 13:55:36 ON 13 APR 2005
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=> s "CARK"
L1          17 "CARK"

=> s "cardiac-related"
L2        1949 "CARDIAC-RELATED"

=> s ankyrin(2w)repeat
L3        4025 ANKYRIN(2W) REPEAT

=> s l2 and l3
L4           4 L2 AND L3

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5             3 DUP REM L4 (1 DUPLICATE REMOVED)

=> d 1-3 ibib ab

L5   ANSWER 1 OF 3  BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2003-13047  BIOTECHDS
TITLE:             Novel isolated cardiac-related
                   ankyrin-repeat protein kinase polypeptide,
                   useful for treating cellular growth related disorders which
                   include cardiovascular disorders and proliferative and/or
                   differentiative disorders;
                      vector-mediated gene transfer and expression in host cell
                      for recombinant protein production for use in disease
                      diagnosis, gene therapy and pharmacogenomics
AUTHOR:            RAJU J
PATENT ASSIGNEE:   MILLENNIUM PHARM INC
PATENT INFO:       WO 2003020912 13 Mar 2003
APPLICATION INFO:  WO 2002-US28300 4 Sep 2002
PRIORITY INFO:     US 2001-947199 5 Sep 2001; US 2001-947199 5 Sep 2001
DOCUMENT TYPE:     Patent
LANGUAGE:          English
```

OTHER SOURCE: WPI: 2003-290188 [28]

AB DERWENT ABSTRACT:

NOVELTY - An isolated **cardiac-related ankyrin -repeat** protein kinase (CARK) polypeptide (I), comprising an allelic variant of a polypeptide having a sequence (S1) of 835 amino acids (aa), encoded by a nucleic acid molecule (NA) that hybridizes to a sequence (S2) of 3025, 2505 or 3026 base pairs, or a polypeptide encoded by a NA 60% homologous to S2, or fragment of S1, where S1 and S2 are given in specification, is new.

DETAILED DESCRIPTION - (I) is selected from a naturally occurring allelic variant of S1 encoded by a NA which hybridizes to NA comprising S2 under stringent conditions, a polypeptide encoded by a NA comprising a sequence which is at least 60% homologous to S2, a fragment comprising at least 15 contiguous (aa)s of S1, and a polypeptide comprising an (aa) sequence which is at least 60% homologous to S1. INDEPENDENT CLAIMS are also included for the following: (1) isolated NA (II) selected from a NA comprising a sequence of S2, a NA which encodes a polypeptide comprising S1, a NA comprising the sequence contained in the plasmid deposited with ATCC as Accession Number PTA-1530, a NA which encodes the naturally occurring allelic variant of S1, a NA comprising a sequence which is at least 60% homologous to S2 or its complement, a NA comprising a fragment of at least 467 nucleotides of S2 or its complement, a NA which encodes a polypeptide comprising a sequence at least about 60% homologous to S1, and a NA which encodes a fragment of S1, where the fragment comprises at least 15 contiguous (aa)s of S1; (2) an isolated NA which hybridizes to (II) under stringent conditions; (3) isolated NA comprising a sequence which is complementary to the sequence of (II); (4) isolated NA comprising (II), and a nucleotide sequence encoding a heterologous polypeptide; (5) vector (III) comprising (II); (6) host cell (HC) transfected with (III); (7) antibody (IV) which selectively binds (I); (8) production of (I); (9) detecting (M1) the presence of (II) in a sample by contacting the sample with a nucleic acid probe or primer which selectively hybridizes to (II), and determining whether the probe or primer binds to (II) in the sample; (10) kit (V) comprising a compound which selectively binds to (I) or hybridizes to (II), and instructions for use; and (11) modulating (M2) the activity of (I) by contacting (I) or a cell expressing (I) with a compound which binds to (I).

WIDER DISCLOSURE - Also disclosed are: (1) isolated NA antisense to (II); (2) diagnostic assay for identifying the presence or absence of a genetic alteration characterized by at least one of aberrant modification or mutation of a gene encoding a CARK protein, mis-regulation of the gene, and aberrant post-translational modification of a CARK protein; (3) nucleic acid molecule that differs from S2, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530; (4) a non-human ortholog of (I); (5) nucleic acid molecule encoding (I) that contains changes in (aa) residues that are not essential for activity; (6) CARK chimeric or fusion proteins; and (7) agent which modulates expression or activity of (I).

BIOTECHNOLOGY - Preparation: (I) is produced by culturing HC in an appropriate culture medium to produce (I) (claimed). Preferred Polypeptide: (I) further comprises heterologous (aa) sequences. Preferred Vector: (III) is an expression vector. Preferred Method: In M1, the sample comprises mRNA molecules and is contacted with a nucleic acid probe.

ACTIVITY - Cardiant; Hypotensive; Cytostatic. No biological data is given.

MECHANISM OF ACTION - Gene therapy.

USE - (IV) is useful for detecting the presence of (I) in a sample by contacting the sample with (IV), and determining whether (IV) binds to (I) in the sample. (I) is useful for identifying a compound which binds to (I) by contacting (I), or a cell expressing (I) with a test compound, and determining whether (I) binds to the test compound. (I) is useful for identifying a compound which modulates the activity of (I) by contacting

(I) with a test compound and determining the effect of the test compound on the activity of (I) (claimed). (I) or (II) is useful as modulating agents for regulating a variety of cellular processes, e.g., cardiac cellular process, for modulating the phosphorylation state of a CARK molecule or one or more proteins involved in cellular growth or differentiation, for modulating cell behavior or as targets and therapeutic agents controlling cardiac cell proliferation, differentiation, hypertrophy and migration, for modulating intra-or inter-cellular signaling and/or gene transcription, for modulating cell proliferation, growth, differentiation, survival and/or migration, for regulating transmission of signals from cellular receptors, for modulating entry of cells, e.g., cardiac precursor cells, into mitosis, or for regulating cytoskeletal function. (I) or (II) is useful for treating cellular growth related disorders which include cardiovascular disorders (such as heart failure, hypertension), and proliferative and/or differentiative disorders (such as cancer). (I), (II) or (IV) is useful in screening assays, detection assays (e.g., chromosomal mapping, tissue typing, forensic biology), predictive medicine (e.g., diagnostic assays, prognostic assays, monitoring clinical trials and pharmacogenomics), and in methods of treatment (e.g., therapeutic and prophylactic). (I) is useful as an immunogen to generate antibodies that bind (I). (I) is useful to screen for naturally occurring CARK substrates, and to screen for drugs or compounds which modulate CARK activity. (I) is useful as a bait protein in a yeast two-hybrid or three-hybrid assay and to identify other proteins which bind to or interact with CARK and or involved in the CARK activity. (II) is useful as hybridization probe to identify (II), or as polymerase chain reaction (PCR) primer for the amplification or mutation of (II). (II) is useful in gene therapy, to express (I), to detect CARK mRNA or a genetic alteration in a CARK gene, and to modulate CARK activity. (II) is useful to map their respective genes on a chromosome, e.g. to locate gene regions associated with genetic disease or to associate CARK with the disease, to identify an individual from a minute biological sample (tissue typing), and to aid in forensic identification of the biological sample. (I) or (II) is useful as a query sequence to perform a search against public databases to, for example, identify other family members or related sequences. HC is useful for producing non-human transgenic animals. (IV) is useful to isolate and purify (I), to detect (I) and to diagnostically monitor protein levels in tissue as part of a clinical testing procedure.

ADMINISTRATION - A pharmaceutical composition comprising (I), (II) or (V) is administered by parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), transmucosal, or rectal route at a dose of 0.001-30 mg/kg, preferably 1-10 mg/kg, more preferably 5-6 mg/kg.

EXAMPLE - Identification and characterization of the genes encoding human **cardiac-related ankyrin-repeat** protein kinase (CARK) and rat CARK was as follows: The human CARK gene was isolated from cDNA library which was prepared from tissue obtained from subjects suffering from congestive heart failure of ischemic and idiopathic origin. Briefly, a cardiac tissue sample was obtained from a biopsy of four patients suffering from congestive heart failure. mRNA was isolated from the cardiac tissue and a cDNA library was prepared. Positive clones were isolated from these libraries using appropriate primers. The sequence of the positive clone was determined and found to contain an open reading frame. The nucleotide sequence encoding the human CARK protein comprised about 3025 nucleic acids. The protein encoded by this nucleic acid comprised abut 835 (aa)s. A clone containing the rat CARK cDNA was also identified. The nucleotide sequence encoding the rat CARK protein comprised about 3026 nucleic acids. The protein encoded by this nucleic acid comprised about 835 (aa)s. (158 pages)

L5 ANSWER 2 OF 3 HCAPLUS

ACCESSION NUMBER: 2002:696560 HCAPLUS
DOCUMENT NUMBER: 137:227755
TITLE: Protein and cDNA sequences of novel human and rat CARK (**cardiac-related ankyrin repeat** protein kinase) and uses thereof
INVENTOR(S): Raju, Jeyaseelan
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 94 pp., Cont.-in-part of U.S. Ser. No. 458,457.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002127684	A1	20020912	US 2001-947199	20010905
US 6660490	B2	20031209		
US 6261818	B1	20010717	US 1999-291839	19990414
US 6500654	B1	20021231	US 1999-458457	19991210
WO 2003020912	A2	20030313	WO 2002-US28300	20020904
WO 2003020912	A3	20030828		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1430070	A2	20040623	EP 2002-757606	20020904
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
US 2004110232	A1	20040610	US 2003-626173	20030724

PRIORITY APPLN. INFO.:

US 1998-111938P	P	19981211
US 1999-291839	A2	19990414
US 1999-458457	A2	19991210
US 2001-947199	A	20010905
WO 2002-US28300	W	20020904

AB The invention provides human and rat protein and cDNA sequences encoding CARK (**cardiac-related ankyrin repeat** protein kinase). The invention also provides antisense nucleic acid mols., recombinant expression vectors containing CARK nucleic acid mols., host cells into which the expression vectors have been introduced, and nonhuman transgenic animals in which a CARK gene has been introduced or disrupted. The invention still further provides isolated CARK proteins, fusion proteins, antigenic peptides and anti-CARK antibodies. Diagnostic methods utilizing compns. of the invention are also provided.

L5 ANSWER 3 OF 3 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
DUPLICATE 1
ACCESSION NUMBER: 2000-11607 BIOTECHDS
TITLE: New polynucleotide encoding **cardiac-related ankyrin-repeat** protein-kinase, useful for treating disorders such as cardiovascular disorders, e.g. heart failure and cell differentiation disorders, e.g. cancer
;
vector-mediated gene transfer and expression in host cell, antibody, DNA probe and DNA primer

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AUTHOR:            Raju J
PATENT ASSIGNEE:   Millennium-Pharm.
LOCATION:          Cambridge, MA, USA.
PATENT INFO:       WO 2000034330 15 Jun 2000
APPLICATION INFO:  WO 1999-US29465 10 Dec 1999
PRIORITY INFO:     US 1999-291839 14 Apr 1999; US 1998-111938 11 Dec 1998
DOCUMENT TYPE:     Patent
LANGUAGE:          English
OTHER SOURCE:      WPI: 2000-431275 [37]
AB     A polynucleotide encoding a cardiac-related
       ankyrin-repeat protein-kinase (EC-2.7.1.37) (CARK)
       containing a sequence of 3,025, 2,505, 3,026 or 2,505 bp as defined in
       the specification, is new.  Also claimed are: a nucleic encoding a
       protein of 835 amino acids; an expression vector; a host cell; a method
       of producing the protein; an antibody; a method for detecting the
       presence of the protein; a method for detecting the presence of the
       polynucleotide using a DNA probe or DNA primer; a kit containing a
       compound that specifically binds to the protein or polynucleotide; a
       method for identifying a compound that specifically binds to the protein;
       a method for modulating the activity of the protein; and a method for
       identifying a compound which modulates that activity of the protein.  The
       polynucleotides is useful for detecting nucleic acid molecule especially
       mRNA in a sample, CARK encoded by the polynucleotide is useful for
       treating disorders associated with upregulation or downregulation of
       cellular proliferation such as disorders concerned with cardiovascular
       disorders and disorders associated with differentiation of cells such as
       cancer and sarcoma.  (161pp)


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     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 13:55:36 ON 13 APR 2005
L1            17 S "CARK"
L2          1949 S "CARDIAC-RELATED"
L3          4025 S ANKYRIN(2W)REPEAT
L4             4 S L2 AND L3
L5             3 DUP REM L4 (1 DUPLICATE REMOVED)

=> dup rem l1
PROCESSING COMPLETED FOR L1
L6            15 DUP REM L1 (2 DUPLICATES REMOVED)

=> d 1-15 ibib ab

L6     ANSWER 1 OF 15  BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
       DUPLICATE 1
ACCESSION NUMBER:  2005-09368  BIOTECHDS
TITLE:             Identifying a subject at risk of melanoma by detecting
                   presence or absence of a polymorphic variation associated
                   with melanoma, where the presence of polymorphic variations
                   is indicative of the subject being at risk of melanoma;
                      using DNA microarray and drug screening for tumor
                      prevention, therapy and pharmacogenetics
AUTHOR:            ROTH R B; NELSON M R; KAMMERER S M; BRAUN A; HOYAL-WRIGHTSON
                   C R
PATENT ASSIGNEE:   SEQUENOM INC
PATENT INFO:       WO 2005017176 24 Feb 2005
APPLICATION INFO:  WO 2004-US14238 5 May 2004
PRIORITY INFO:     US 2003-704513 6 Nov 2003; US 2003-489703 23 Jul 2003
DOCUMENT TYPE:     Patent
```

LANGUAGE: English
OTHER SOURCE: WPI: 2005-182387 [19]
AB DERWENT ABSTRACT:

NOVELTY - Identifying a subject at risk of melanoma comprising detecting the presence or absence of a polymorphic variation associated with melanoma, where the presence of the one or more polymorphic variations is indicative of the subject being at risk of melanoma, is new.

DETAILED DESCRIPTION - Identifying a subject at risk of melanoma comprises detecting the presence or absence of a polymorphic variation associated with melanoma at one or more positions selected from rs6481845, rs10643659, rs7475391, rs7475394, rs7475396, rs9418057, rs5784335, rs2429390, rs7209331, rs4968706, rs8072984, rs9896444, rs4968617, rs7350907, rs8072519, rs6467914, rs3064869, rs10555175, rs6956848, position 63624 in a sequence comprising a fully defined 89700 bp (SEQ ID NO. 6) given in the specification, position 65039 in SEQ ID NO. 6, rs489941, rs496008, rs4650251, rs531412, rs3765654, rs6660350, position 206 in a sequence comprising a fully defined 97400 bp (SEQ ID NO. 5) given in the specification, rs5924619, rs5924564, rs4828523, rs5924569, rs2052763, rs1549529, rs5924573, rs4240072, rs5924580, rs4828544, rs5969758, rs1965051, rs1426800, rs1365529, rs5924545, rs5969761, rs6629202, rs5924584, rs1365530, rs6527769, rs2382813, rs2033120, rs2162394, rs1346246, rs1365527, rs4828524, rs5924588, rs5969764, rs5924589, rs5924590, rs5924593, rs4828547, rs5969768, rs4828526, rs5924595, rs5924549, rs5969769, rs4007744, rs2891073, rs5924599, rs1549531, rs5924601, rs5901609, rs5969739, rs5924602, rs1426798, rs4828550, rs5924603, rs1807947, rs2382814, rs5924606 and position 25216 in a sequence comprising 213300 bp (SEQ ID NO. 7) given in the specification, where the presence of the one or more polymorphic variations is indicative of the subject being at risk of melanoma. INDEPENDENT CLAIMS are also included for: (1) identifying a polymorphic variation associated with melanoma proximal to an incident polymorphic variation associated with melanoma; (2) an isolated nucleic acid which comprises a portion of or all of a nucleotide sequence comprising fully defined 68400-213300 base pairs sequences (SEQ ID NO. 3, 4, 5, 6, and/or 7) given in the specification, and comprises one or more polymorphic variations selected from an adenine at position 16727 in SEQ ID NO. 3, a guanine at position 36589 in SEQ ID NO. 4, a thymine at position 44544 in SEQ ID NO. 4, a guanine at position 48304 in SEQ ID NO. 4, a guanine at position 53843 in SEQ ID NO. 6, a guanine at position 63624 in SEQ ID NO. 6, an adenine-thymine deletion at position 65039 in SEQ ID NO. 6, a guanine at position 206 in SEQ ID NO. 5, an adenine at position 9261 in SEQ ID NO. 5, a thymine at position 37592 in SEQ ID NO. 5, a guanine at position 10537 in SEQ ID NO. 7, a cytosine at position 25216 in SEQ ID NO. 7, or a thymine at position 119368 in SEQ ID NO. 7; (3) an oligonucleotide comprising a nucleotide sequence complementary to a portion of the nucleotide sequence above, where the 3' end of the oligonucleotide is adjacent to a polymorphic variation; (4) a microarray comprising the isolated nucleic acid linked to a solid support; (5) an isolated polypeptide encoded by the isolated nucleic acid sequence; (6) genotyping a nucleic acid; (7) identifying a candidate molecule that modulates cell proliferation; (8) treating melanoma in a subject; and (9) treating melanoma in a subject or preventing melanoma in a subject.

WIDER DISCLOSURE - A composition comprising a melanoma cell and/or a NRP1, NID2, ENDO180, CDK10, FPGT, **CARK**, PCLO, or REPS2.

BIOTECHNOLOGY - Preferred Method: Identifying a subject at risk of melanoma further comprises obtaining the nucleic acid sample from the subject. A polymorphic variation is detected at one or more positions selected from: (a) rs6481845, rs10643659, rs7475391, rs7475394, rs7475396, rs9418057, or rs5784335; (b) rs2429390, rs7209331, rs4968706, rs8072984, rs9896444, rs4968617, rs7350907, or rs8072519; (c) rs6467914, rs3064869, rs10555175, rs6956848, position 63624 in SEQ ID NO. 6, or position 65039 in SEQ ID NO. 6; (d) rs489941, rs496008, rs4650251, rs531412, rs3765654, rs6660350, or position 206 in SEQ ID NO. 5; or (e)

rs5924619, rs5924564, rs4828523, rs5924569, rs2052763, rs1549529, rs5924573, rs4240072, rs5924580, rs4828544, rs5969758, rs1965051, rs1426800, rs1365529, rs5924545, rs5969761, rs6629202, rs5924584, rs1365530, rs6527769, rs2382813, rs2033120, rs2162394, rs1346246, rs1365527, rs4828524, rs5924588, rs5969764, rs5924589, rs5924590, rs5924593, rs4828547, rs5969768, rs4828526, rs5924595, rs5924549, rs5969769, rs4007744, rs2891073, rs5924599, rs1549531, rs5924601, rs5901609, rs5969739, rs5924602, rs1426798, rs4828550, rs5924603, rs1807947, rs2382814, rs5924606, or position 25216 in SEQ ID NO. 7. One or more polymorphic variations are detected at one or more positions in linkage disequilibrium with a polymorphic variation at one or more of the positions given above. Detecting the presence or absence of the one or more polymorphic variations comprises: (a) hybridizing an oligonucleotide to the nucleic acid sample, where the oligonucleotide is complementary to a nucleotide sequence in the nucleic acid and hybridizes to a region adjacent to the polymorphic variation; (b) extending the oligonucleotide in the presence of one or more nucleotides, yielding extension products; and (c) detecting the presence or absence of a polymorphic variation in the extension products. The subject is a human. Identifying a polymorphic variation associated with melanoma proximal to an incident polymorphic variation associated with melanoma comprises: (a) identifying a polymorphic variation proximal to the incident polymorphic variation associated with melanoma, where the incident polymorphic variation is at a position selected from those given above; and(b) determining the presence or absence of an association of the proximal polymorphic variant with melanoma. The proximal polymorphic variation is within a region between 5 kb 5' of the incident polymorphic variation and 5 kb 3' of the incident polymorphic variation. The method further comprises determining whether the proximal polymorphic variation is at a position in linkage disequilibrium with the incident polymorphic variation. It also comprises identifying a second polymorphic variation proximal to the identified proximal polymorphic variation associated with melanoma and determining if the second proximal polymorphic variation is associated with melanoma. The second proximal polymorphic variant is within a region between 5 kb 5' of the incident polymorphic variation and 5 kb 3' of the proximal polymorphic variation associated with melanoma. Genotyping a nucleic acid at a position selected from position 16727 in SEQ ID NO. 3, position 36589 in SEQ ID NO. 4, position 44544 in SEQ ID NO. 4, position 48304 in SEQ ID NO. 4, position 53843 in SEQ ID NO. 6, position 63624 in SEQ ID NO. 6, position 65039 in SEQ ID NO. 6, position 206 in SEQ ID NO. 5, position 9261 in SEQ ID NO. 5, position 37592 in SEQ ID NO. 5, position 10537 in SEQ ID NO. 7, position 25216 in SEQ ID NO. 7, or position 119368 in SEQ ID NO. 7. The method comprises genotyping the nucleic acid at position 16727 in SEQ ID NO. 3. It also comprises genotyping the nucleic acid at a position selected from position 36589 in SEQ ID NO. 4, position 44544 in SEQ ID NO. 4, or position 48304 in SEQ ID NO. 4. It further comprises genotyping the nucleic acid at a position selected from position 53843 in SEQ ED NO: 6, position 63624 in SEQ ID NO. 6, or position 65039 in SEQ ID NO. 6. The method also comprises genotyping the nucleic acid at a position selected from position 206 in SEQ ID NO. 5, position 9261 in SEQ ID NO. 5, or position 37592 in SEQ ID NO. 5. It further comprises genotyping the nucleic acid at a position selected from position 10537 in SEQ ID NO. 7, position 25216 in SEQ ID NO. 7, or position 119368 in SEQ ID NO. 7. Identifying a candidate molecule that modulates cell proliferation comprises: (a) introducing a test molecule to a system which comprises one or more cells and a nucleic acid comprising one or more polymorphic variations at one or more positions selected from those given above; and (b) determining whether cell proliferation is increased or decreased compared to a system not containing the test molecule, where a increased or decreased cell proliferation identifies the test molecule as a candidate molecule that modulates cell proliferation. The system is an animal, preferably one or more cells. Treating melanoma in a subject comprises administering a

candidate molecule identified above to a subject in need, where the candidate molecule treats melanoma in the subject. Treating melanoma in a subject or preventing melanoma in a subject comprises detecting the presence or absence of one or more polymorphic variations at one or more positions selected from those given above, and administering a melanoma treatment or administering a melanoma preventative to a subject in need based upon the presence or absence of the one or more polymorphic variations in the nucleic acid sample. The method further comprises extracting and analyzing a tissue biopsy sample from the subject. The treatment is one or more selected from administering cisplatin, administering carmustine, administering vinblastine, administering vincristine, administering bleomycin, administering a combination of those given above, or surgery. The preventative reduces ultraviolet (UV) light exposure to the subject. Preferred Nucleic Acid: The isolated nucleic acid comprises an adenine at position 16727 in SEQ ID NO. 3. It also comprises a polymorphic variation selected from a guanine at position 36589 in SEQ ID NO. 4, a thymine at position 44544 in SEQ ID NO. 4, or a guanine at position 48304 in SEQ ID NO. 4. It further comprises a polymorphic variation selected from a guanine at position 53843 in SEQ ID NO. 6, a guanine at position 63624 in SEQ ID NO. 6, or an adenine-thymine deletion at position 65039 in SEQ ID NO. 6. It also comprises a polymorphic variation selected from a guanine at position 206 in SEQ ID NO. 5, an adenine at position 9261 in SEQ ID NO. 5, or a thymine at position 37592 in SEQ ID NO. 5. The isolated nucleic acid also comprises a polymorphic variation selected from a guanine at position 10537 in SEQ ID NO. 7, a cytosine at position 25216 in SEQ ID NO. 7, or a thymine at position 119368 in SEQ ID NO. 7.

ACTIVITY - Cytostatic. No biological data given.

MECHANISM OF ACTION - Gene Therapy.

USE - The methods are useful for identifying a subject at risk of melanoma, treating melanoma in a subject, or preventing melanoma in a subject.

ADMINISTRATION - Dosage is 0.001-30 mg/kg. Administration can be through parenteral, e.g. intravenous, intradermal, subcutaneous, oral (e.g. inhalation), transdermal (topical), transmucosal, or rectal routes.

EXAMPLE - No relevant example given.(418 pages)

L6 ANSWER 2 OF 15 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2005:189110 SCISEARCH
THE GENUINE ARTICLE: 895QW
TITLE: Evidence for the operation of alternative electron transport routes through photosystem I in intact barley leaves under weak and moderate white light
AUTHOR: Bukhov N G (Reprint); Egorova E A
CORPORATE SOURCE: Russian Acad Sci, Timiryazev Inst Plant Physiol, Botanicheskaya Ul 35, Moscow 127276, Russia (Reprint); Russian Acad Sci, Timiryazev Inst Plant Physiol, Moscow 127276, Russia
COUNTRY OF AUTHOR: Russia
SOURCE: RUSSIAN JOURNAL OF PLANT PHYSIOLOGY, (JAN-FEB 2005) Vol. 52, No. 1, pp. 1-6.
Publisher: MAIK NAUKA/INTERPERIODICA, C/O KLUWER ACADEMIC-PLENUM PUBLISHERS, 233 SPRING ST, NEW YORK, NY 10013-1578 USA.
ISSN: 1021-4437.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 23

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The functioning of alternative routes of photosynthetic electron transport was analyzed from the kinetics of dark reduction of P700(+), an oxidized primary donor of PSI, in barley (Hordeum vulgare L.) leaves

irradiated by white light of various intensities. Redox changes of P700 were monitored as absorbance changes at 830 nm using PAM 101 specialized device. Irradiation of dark-adapted leaves caused a gradual P700(+) accumulation, and the steady-state level of oxidized P700 increased with intensity of actinic light. The kinetics of P700(+) **Cark** reduction after a pulse of strong actinic light, assayed from the absorbance changes at 830 nm, was fitted by a single exponential term with a halftime of 10-12 ins. Two slower components were observed in the kinetics of P700(+) dark reduction after leaf irradiation by attenuated actinic light. The contribution of slow components to P700(+) reduction increased with the decrease in actinic light intensity. Two slow components characterized by halftimes similar to those observed after leaf irradiation by weak white light were found in the kinetics of dark reduction of P700(+) oxidized in leaves with far-red light specifically absorbed by PSI. The treatment of leaves with methyl viologen, an artificial PSI electron acceptor, significantly accelerated the accumulation of P70C(+) under light. At the same time, the presence of methyl viologen, which inhibits ferredoxin-dependent electron transport around PSI, did not affect three components of the kinetics of P700(+) dark reduction obtained after irradiations with various actinic light intensities. It was concluded that some part of PSI reaction centers was not reduced by electron transfer from PSII under weak or moderate intensities of actinic light. In this population of PSI centers, P700(+) was reduced via alternative electron transport routes. Insensitivity of the kinetics of P700(+) dark reduction to methyl viologen evidences that the input of electrons to PSI from the reductants (NADPH or NADH) localized in the chloroplast stroma was effective under those light conditions.

L6 ANSWER 3 OF 15 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:74544 BIOSIS
DOCUMENT NUMBER: PREV200400077782
TITLE: **CARK** protein and nucleic acid molecules and uses therefor.
AUTHOR(S): Raju, Jeyaseelan [Inventor, Reprint Author]
CORPORATE SOURCE: ASSIGNEE: Millennnium Pharmaceuticals, Inc., Cambridge, MA, USA
PATENT INFORMATION: US 6660490 December 09, 2003
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Dec 9 2003) Vol. 1277, No. 2. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Feb 2004
Last Updated on STN: 4 Feb 2004

AB The invention provides isolated nucleic acids molecules, designated **CARK** nucleic acid molecules. The invention also provides antisense nucleic acid molecules, recombinant expression vectors containing **CARK** nucleic acid molecules, host cells into which the expression vectors have been introduced, and nonhuman transgenic animals in which a **CARK** gene has been introduced or disrupted. The invention still further provides isolated **CARK** proteins, fusion proteins, antigenic peptides and anti-**CARK** antibodies. Diagnostic methods utilizing compositions of the invention are also provided.

L6 ANSWER 4 OF 15 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2003-13047 BIOTECHDS
TITLE: Novel isolated cardiac-related ankyrin-repeat protein kinase polypeptide, useful for treating cellular growth related disorders which include cardiovascular disorders and proliferative and/or differentiative disorders;

vector-mediated gene transfer and expression in host cell for recombinant protein production for use in disease diagnosis, gene therapy and pharmacogenomics

AUTHOR: RAJU J
PATENT ASSIGNEE: MILLENNIUM PHARM INC
PATENT INFO: WO 2003020912 13 Mar 2003
APPLICATION INFO: WO 2002-US28300 4 Sep 2002
PRIORITY INFO: US 2001-947199 5 Sep 2001; US 2001-947199 5 Sep 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2003-290188 [28]

AB DERWENT ABSTRACT:

NOVELTY - An isolated cardiac-related ankyrin-repeat protein kinase (**CARK**) polypeptide (I), comprising an allelic variant of a polypeptide having a sequence (S1) of 835 amino acids (aa), encoded by a nucleic acid molecule (NA) that hybridizes to a sequence (S2) of 3025, 2505 or 3026 base pairs, or a polypeptide encoded by a NA 60% homologous to S2, or fragment of S1, where S1 and S2 are given in specification, is new.

DETAILED DESCRIPTION - (I) is selected from a naturally occurring allelic variant of S1 encoded by a NA which hybridizes to NA comprising S2 under stringent conditions, a polypeptide encoded by a NA comprising a sequence which is at least 60% homologous to S2, a fragment comprising at least 15 contiguous (aa)s of S1, and a polypeptide comprising an (aa) sequence which is at least 60% homologous to S1. INDEPENDENT CLAIMS are also included for the following: (1) isolated NA (II) selected from a NA comprising a sequence of S2, a NA which encodes a polypeptide comprising S1, a NA comprising the sequence contained in the plasmid deposited with ATCC as Accession Number PTA-1530, a NA which encodes the naturally occurring allelic variant of S1, a NA comprising a sequence which is at least 60% homologous to S2 or its complement, a NA comprising a fragment of at least 467 nucleotides of S2 or its complement, a NA which encodes a polypeptide comprising a sequence at least about 60% homologous to S1, and a NA which encodes a fragment of S1, where the fragment comprises at least 15 contiguous (aa)s of S1; (2) an isolated NA which hybridizes to (II) under stringent conditions; (3) isolated NA comprising a sequence which is complementary to the sequence of (II); (4) isolated NA comprising (II), and a nucleotide sequence encoding a heterologous polypeptide; (5) vector (III) comprising (II); (6) host cell (HC) transfected with (III); (7) antibody (IV) which selectively binds (I); (8) production of (I); (9) detecting (M1) the presence of (II) in a sample by contacting the sample with a nucleic acid probe or primer which selectively hybridizes to (II), and determining whether the probe or primer binds to (II) in the sample; (10) kit (V) comprising a compound which selectively binds to (I) or hybridizes to (II), and instructions for use; and (11) modulating (M2) the activity of (I) by contacting (I) or a cell expressing (I) with a compound which binds to (I).

WIDER DISCLOSURE - Also disclosed are: (1) isolated NA antisense to (II); (2) diagnostic assay for identifying the presence or absence of a genetic alteration characterized by at least one of aberrant modification or mutation of a gene encoding a **CARK** protein, mis-regulation of the gene, and aberrant post-translational modification of a **CARK** protein; (3) nucleic acid molecule that differs from S2, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530; (4) a non-human ortholog of (I); (5) nucleic acid molecule encoding (I) that contains changes in (aa) residues that are not essential for activity; (6) **CARK** chimeric or fusion proteins; and (7) agent which modulates expression or activity of (I).

BIOTECHNOLOGY - Preparation: (I) is produced by culturing HC in an appropriate culture medium to produce (I) (claimed). Preferred Polypeptide: (I) further comprises heterologous (aa) sequences. Preferred Vector: (III) is an expression vector. Preferred Method: In M1, the

sample comprises mRNA molecules and is contacted with a nucleic acid probe.

ACTIVITY - Cardiant; Hypotensive; Cytostatic. No biological data is given.

MECHANISM OF ACTION - Gene therapy.

USE - (IV) is useful for detecting the presence of (I) in a sample by contacting the sample with (IV), and determining whether (IV) binds to (I) in the sample. (I) is useful for identifying a compound which binds to (I) by contacting (I), or a cell expressing (I) with a test compound, and determining whether (I) binds to the test compound. (I) is useful for identifying a compound which modulates the activity of (I) by contacting (I) with a test compound and determining the effect of the test compound on the activity of (I) (claimed). (I) or (II) is useful as modulating agents for regulating a variety of cellular processes, e.g., cardiac cellular process, for modulating the phosphorylation state of a **CARK** molecule or one or more proteins involved in cellular growth or differentiation, for modulating cell behavior or as targets and therapeutic agents controlling cardiac cell proliferation, differentiation, hypertrophy and migration, for modulating intra-or inter-cellular signaling and/or gene transcription, for modulating cell proliferation, growth, differentiation, survival and/or migration, for regulating transmission of signals from cellular receptors, for modulating entry of cells, e.g., cardiac precursor cells, into mitosis, or for regulating cytoskeletal function. (I) or (II) is useful for treating cellular growth related disorders which include cardiovascular disorders (such as heart failure, hypertension), and proliferative and/or differentiative disorders (such as cancer). (I), (II) or (IV) is useful in screening assays, detection assays (e.g., chromosomal mapping, tissue typing, forensic biology), predictive medicine (e.g., diagnostic assays, prognostic assays, monitoring clinical trials and pharmacogenomics), and in methods of treatment (e.g., therapeutic and prophylactic). (I) is useful as an immunogen to generate antibodies that bind (I). (I) is useful to screen for naturally occurring **CARK** substrates, and to screen for drugs or compounds which modulate **CARK** activity. (I) is useful as a bait protein in a yeast two-hybrid or three-hybrid assay and to identify other proteins which bind to or interact with **CARK** and or involved in the **CARK** activity. (II) is useful as hybridization probe to identify (II), or as polymerase chain reaction (PCR) primer for the amplification or mutation of (II). (II) is useful in gene therapy, to express (I), to detect **CARK** mRNA or a genetic alteration in a **CARK** gene, and to modulate **CARK** activity. (II) is useful to map their respective genes on a chromosome, e.g. to locate gene regions associated with genetic disease or to associate **CARK** with the disease, to identify an individual from a minute biological sample (tissue typing), and to aid in forensic identification of the biological sample. (I) or (II) is useful as a query sequence to perform a search against public databases to, for example, identify other family members or related sequences. HC is useful for producing non-human transgenic animals. (IV) is useful to isolate and purify (I), to detect (I) and to diagnostically monitor protein levels in tissue as part of a clinical testing procedure.

ADMINISTRATION - A pharmaceutical composition comprising (I), (II) or (V) is administered by parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), transmucosal, or rectal route at a dose of 0.001-30 mg/kg, preferably 1-10 mg/kg, more preferably 5-6 mg/kg.

EXAMPLE - Identification and characterization of the genes encoding human cardiac-related ankyrin-repeat protein kinase (**CARK**) and rat **CARK** was as follows: The human **CARK** gene was isolated from cDNA library which was prepared from tissue obtained from subjects suffering from congestive heart failure of ischemic and idiopathic origin. Briefly, a cardiac tissue sample was obtained from a biopsy of four patients suffering from congestive heart failure. mRNA was

isolated from the cardiac tissue and a cDNA library was prepared. Positive clones were isolated from these libraries using appropriate primers. The sequence of the positive clone was determined and found to contain an open reading frame. The nucleotide sequence encoding the human **CARK** protein comprised about 3025 nucleic acids. The protein encoded by this nucleic acid comprised abut 835 (aa)s. A clone containing the rat **CARK** cDNA was also identified. The nucleotide sequence encoding the rat **CARK** protein comprised about 3026 nucleic acids. The protein encoded by this nucleic acid comprised about 835 (aa)s. (158 pages)

L6 ANSWER 5 OF 15 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:85983 BIOSIS
DOCUMENT NUMBER: PREV200300085983
TITLE: **CARK** protein and nucleic acid molecules and uses therefor.
AUTHOR(S): Raju, Jeyaseelan [Inventor, Reprint Author]
CORPORATE SOURCE: ASSIGNEE: Millennium Pharmaceuticals, Inc.
PATENT INFORMATION: US 6500654 December 31, 2002
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Dec 31 2002) Vol. 1265, No. 5. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Feb 2003
Last Updated on STN: 6 Feb 2003

AB The invention provides isolated nucleic acids molecules, designated **CARK** nucleic acid molecules. The invention also provides antisense nucleic acid molecules, recombinant expression vectors containing **CARK** nucleic acid molecules, host cells into which the expression vectors have been introduced, and nonhuman transgenic animals in which a **CARK** gene has been introduced or disrupted. The invention still further provides isolated **CARK** proteins, fusion proteins, antigenic peptides and anti-**CARK** antibodies. Diagnostic methods utilizing compositions of the invention are also provided.

L6 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:696560 HCAPLUS
DOCUMENT NUMBER: 137:227755
TITLE: Protein and cDNA sequences of novel human and rat **CARK** (cardiac-related ankyrin repeat protein kinase) and uses thereof
INVENTOR(S): Raju, Jeyaseelan
PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 94 pp., Cont.-in-part of U.S. Ser. No. 458,457.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002127684	A1	20020912	US 2001-947199	20010905
US 6660490	B2	20031209		
US 6261818	B1	20010717	US 1999-291839	19990414
US 6500654	B1	20021231	US 1999-458457	19991210
WO 2003020912	A2	20030313	WO 2002-US28300	20020904
WO 2003020912	A3	20030828		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
EP 1430070 A2 20040623 EP 2002-757606 20020904
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK
US 2004110232 A1 20040610 US 2003-626173 20030724
PRIORITY APPLN. INFO.: US 1998-111938P P 19981211
US 1999-291839 A2 19990414
US 1999-458457 A2 19991210
US 2001-947199 A 20010905
WO 2002-US28300 W 20020904

AB The invention provides human and rat protein and cDNA sequences encoding **CARK** (cardiac-related ankyrin repeat protein kinase). The invention also provides antisense nucleic acid mols., recombinant expression vectors containing **CARK** nucleic acid mols., host cells into which the expression vectors have been introduced, and nonhuman transgenic animals in which a **CARK** gene has been introduced or disrupted. The invention still further provides isolated **CARK** proteins, fusion proteins, antigenic peptides and anti-**CARK** antibodies. Diagnostic methods utilizing compns. of the invention are also provided.

L6 ANSWER 7 OF 15 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:341659 SCISEARCH
THE GENUINE ARTICLE: 540HT
TITLE: Anemia prevention and control in four central Asian republics and Kazakhstan
AUTHOR: Gleason G R (Reprint); Sharmanov T
CORPORATE SOURCE: IDPAS, Iron Deficiency Project Advisory Serv, 126 Curtis St, Medford, MA 02155 USA (Reprint); IDPAS, Iron Deficiency Project Advisory Serv, Medford, MA 02155 USA; Nutr Inst Kazakhstan, Almaty 480008, Kazakhstan
COUNTRY OF AUTHOR: USA; Kazakhstan
SOURCE: JOURNAL OF NUTRITION, (APR 2002) Vol. 132, No. 4, Supp. [S], pp. 867S-870S.
Publisher: AMER INST NUTRITION, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
ISSN: 0022-3166.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 0
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Kazakhstan and the central Asian republics of Uzbekistan, the Kyrgyz Republic, Tajikistan and Turkmenistan have developed anemia prevention and control (APC) policies based on multiple interventions, including education and promotion, oral supplementation of high risk groups and fortification of wheat flour with iron and other micronutrients. These national strategies are aimed at reducing the prevalence of anemia and iron deficiency among young children and women of child-bearing age. Strategy development has been assisted by funding and technical assistance from the United Nations Children's Fund (UNICEF) with additional technical support from the International Nutrition Foundation, the United Nations University and various national institutions. These countries have been among the most advanced in adopting national strategies that include multiple interventions in an overall package, and national interest in APC

remains high. However, reviews of APC activities conducted in 2001 suggests the need for modification and enhancement of current efforts and for a shift to national-level actions if these countries are to progress toward current and future goals. Increased commitment and determination, by both national groups and international organizations, are required to achieve and sustain improvement in micronutrient nutrition.

L6 ANSWER 8 OF 15 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:420615 BIOSIS
DOCUMENT NUMBER: PREV200100420615
TITLE: **CARK** protein and nucleic acid molecules and uses therefor.
AUTHOR(S): Raju, Jeyaseelan [Inventor, Reprint author]
CORPORATE SOURCE: Acton, MA, USA
ASSIGNEE: Millennium Pharmaceuticals, Inc.
PATENT INFORMATION: US 6261818 July 17, 2001
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (July 17, 2001) Vol. 1248, No. 3. e-file. CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Sep 2001
Last Updated on STN: 22 Feb 2002

AB The invention provides isolated nucleic acids molecules, designated **CARK** nucleic acid molecules. The invention also provides antisense nucleic acid molecules, recombinant expression vectors containing **CARK** nucleic acid molecules, host cells into which the expression vectors have been introduced, and nonhuman transgenic animals in which a **CARK** gene has been introduced or disrupted. The invention still further provides isolated **CARK** proteins, fusion proteins, antigenic peptides and anti-**CARK** antibodies. Diagnostic methods utilizing compositions of the invention are also provided.

L6 ANSWER 9 OF 15 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
DUPLICATE 2
ACCESSION NUMBER: 2000-11607 BIOTECHDS
TITLE: New polynucleotide encoding cardiac-related ankyrin-repeat protein-kinase, useful for treating disorders such as cardiovascular disorders, e.g. heart failure and cell differentiation disorders, e.g. cancer;
vector-mediated gene transfer and expression in host cell, antibody, DNA probe and DNA primer
AUTHOR: Raju J
PATENT ASSIGNEE: Millennium-Pharm.
LOCATION: Cambridge, MA, USA.
PATENT INFO: WO 2000034330 15 Jun 2000
APPLICATION INFO: WO 1999-US29465 10 Dec 1999
PRIORITY INFO: US 1999-291839 14 Apr 1999; US 1998-111938 11 Dec 1998
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2000-431275 [37]

AB A polynucleotide encoding a cardiac-related ankyrin-repeat protein-kinase (EC-2.7.1.37) (**CARK**) containing a sequence of 3,025, 2,505, 3,026 or 2,505 bp as defined in the specification, is new. Also claimed are: a nucleic encoding a protein of 835 amino acids; an expression vector; a host cell; a method of producing the protein; an antibody; a method for detecting the presence of the protein; a method for detecting the presence of the polynucleotide using a DNA probe or DNA primer; a kit containing a compound that specifically binds to the protein or polynucleotide; a method for identifying a compound that specifically binds to the protein; a method for modulating the activity of the protein; and a method for identifying a compound which modulates that

activity of the protein. The polynucleotides is useful for detecting nucleic acid molecule especially mRNA in a sample, **CARK** encoded by the polynucleotide is useful for treating disorders associated with upregulation or downregulation of cellular proliferation such as disorders concerned with cardiovascular disorders and disorders associated with differentiation of cells such as cancer and sarcoma. (161pp)

L6 ANSWER 10 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:200376 HCAPLUS
DOCUMENT NUMBER: 126:197250
TITLE: Regulation of the O2-evolving mechanism during N2-fixation in the diazotrophic cyanobacterium Cyanothece sp. ATCC 51142
AUTHOR(S): Meunier, Pascal C.; Watters, James W.; Colon-Lopez, Milagros S.; Sherman, L. A.
CORPORATE SOURCE: Department of Biological Sciences, Purdue University, West Lafayette, IN, 47907, USA
SOURCE: Photosynthesis: From Light to Biosphere, Proceedings of the International Photosynthesis Congress, 10th, Montpellier, Fr., Aug. 20-25, 1995 (1995), Volume 2, 389-392. Editor(s): Mathis, Paul. Kluwer: Dordrecht, Neth.
CODEN: 64DFAW
DOCUMENT TYPE: Conference
LANGUAGE: English

AB N2 fixation by C. ATCC 51142 is controlled by a circadian rhythm. The capacity and the properties of O2 production by the S-state mechanism in cultures subjected to 12-h light/**cark** cycles were investigated. The peak of O2 evolution was found to be 12 h out of phase with N2 fixation. These results suggested that the stability of Mn centers in the dark, their sensitivity to the redox state of quinones, the capacity for O2 production, the photoreactivation capacity, and the presence of super-reduced S-states are all modulated in Cyanothece.

L6 ANSWER 11 OF 15 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 92:3159 SCISEARCH
THE GENUINE ARTICLE: GT369
TITLE: THE THEORY OF CYCLOTRON AUTORESONANCE KLYSTRON
AUTHOR: SMIRNOV G T (Reprint)
CORPORATE SOURCE: ACAD SCI USSR, URAL SCI CTR, INST ELECTROPHYS, SVERDLOVSK, USSR (Reprint)
COUNTRY OF AUTHOR: USSR
SOURCE: IZVESTIYA VYSSHIKH UCHEBNYKH ZAVEDENII RADIOFIZIKA, (1991) Vol. 34, No. 2, pp. 177.
ISSN: 0021-3462.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: ENGI
LANGUAGE: Russian
REFERENCE COUNT: 10
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB A cyclotron autoresonance klystron (**CARK**), a new type of cyclotron autoresonance maser, is theoretically investigated. The formulae of efficiency, threshold current and optimum current are obtained with taken intoaccount and initial electron beam energy spread and pitch angle spread. It is shown, that the efficiency of the **CARK**, which is constructed bu the analogy with a two-resonator klystron, may be more than 50%, und the efficiency of the **CARK**, which is consructed bu the analogy with a three-resonator klystron, reaches 60%. The **CARK** realatively intensive to the electron beam quality. For example, in the powerful **CARK** the initial electron beam energy spread and pitch angle spread may amount several per cent without

the sufficient loss of efficiency.

L6 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:562636 HCAPLUS
DOCUMENT NUMBER: 109:162636
TITLE: A catechol electrode based on spinach leaves
AUTHOR(S): Uchiyama, Shunichi; Tamata, Minoru; Tofuku, Yoshinobu; Suzuki, Shuichi
CORPORATE SOURCE: Dep. Environ. Eng., Saitama Inst. Technol., Saitama, 369-02, Japan
SOURCE: Analytica Chimica Acta (1988), 208(1-2), 287-90
CODEN: ACACAM; ISSN: 0003-2670
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Minced spinach leaf (Spinacea oleracea) has a high activity of catechol oxidase (dimerizing) (EC 1.1.3.14), which is utilized for the determination of catechol by coupling the spinach tissue with a Clark oxygen electrode. The calibration graph for catechol is linear over the range 2 + 10-5-8 + 10-4M (relative standard deviation 3%). The sensor retains its enzyme activity for at least 18 days. 4-Methylcatechol and glycolate interfere; glucose and ascorbate do not.

L6 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1985:429158 HCAPLUS
DOCUMENT NUMBER: 103:29158
TITLE: Evaluation of thin film properties by the coulostatic method
AUTHOR(S): Fukunaga, Akihiko; Ueda, Shigetomo; Suzuki, Masayuki
CORPORATE SOURCE: Negishi Refinery Inspect Sect., Nippon Pet. Refinery Co. Ltd., Yokohama, 235, Japan
SOURCE: Kinzoku Hyomen Gijutsu (1985), 36(5), 191-7
CODEN: KZHGAY; ISSN: 0026-0614
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB The differential double layer capacitance and polarization resistance of the vapor-deposited thin films of Al and Al-Cu under various conditions were measured in **Cark** Lubs buffer solution (pH 7.2) by the coulostatic method, and compared with other films and bulk metals. The differential capacitance and polarization resistance represented the surface conditions of the films, therefore they are effective in evaluating the corrosion rate and estimating the depth of oxide films.

L6 ANSWER 14 OF 15 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1983:244189 BIOSIS
DOCUMENT NUMBER: PREV198376001681; BA76:1681
TITLE: DISTRIBUTION OF LARVAL GIZZARD SHAD DOROSOMA-CEPEDIANUM IN LAKE CARL-BLACKWELL OKLAHOMA USA.
AUTHOR(S): DOWNEY P [Reprint author]; TOETZ D
CORPORATE SOURCE: BOX 747, OUACHITA BAPTIST UNIV, ARKADELPHIA, ARKANSAS 71923, USA
SOURCE: American Midland Naturalist, (1983) Vol. 109, No. 1, pp. 23-33.
CODEN: AMNAAF. ISSN: 0003-0031.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
AB Year-class formation in fishes in poorly understood because of the difficulty of estimating abundance of fish larvae. The temporal and spatial distribution of gizzard shad larvae (D. cepedianum) in Lake **Cark** Blackwell (LCB), Oklahoma is described to provide a basis for future efforts at sampling larvae of this important forage fish in

reservoirs. Larvae were sampled with a net (mouth 0.20 m2) towed in front of a boat at night at depths of 0 (surface), 3, 5 and 7 m between April and July 1977. Wind direction and velocity, cited by other workers as decisive in determining fish larval distribution, were related to patterns of larval abundance. Larvae were captured by the gear at a length of .apprx. 5 mm, but were not captured after they reached slightly more than 15 mm .apprx. 10 wk later. Larval density was highest, .apprx. 100 m-3, during late May and early June. Larvae were captured near the surface at the outset and were apparently passively distributed by winds. The rest of the time they were most abundant at 3 m, near the compensation point, suggesting maintenance of a preferred position in the water column. Estimates of larval shad density taken offshore were the same as estimates nearshore in areas of the lake with either very high or low densities. The dendritic configuration of the lake basin precluded prediction of horizontal or vertical patterns of distribution of shad larvae. Accurate estimates of density will be possible only by intensively sampling all areas of the lake throughout the season. Stratified random sampling programs for shad larvae are not now reasonable for dendritic lakes such as LCB.

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L6   ANSWER 15 OF 15  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         1982:51293  HCAPLUS
DOCUMENT NUMBER:          96:51293
TITLE:                    Changes and significance in natural nitrogen-15
                          abundance in residual nitrogen fertilizer studies
AUTHOR(S):                Karamanos, R. E.; Rennie, D. A.
CORPORATE SOURCE:         Dep. Soil Sci., Univ. Saskatchewan, Saskatoon, SK, S7N
                          0W0, Can.
SOURCE:                   Canadian Journal of Soil Science (1981), 61(4), 553-9
                          CODEN: CJSSAR; ISSN: 0008-4271
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
```

AB The systematic decline in δa15N (per mill 15N excess) of plant material with application of fertilizer under field conditions was verified in a growth chamber experiment with wheat on Orthic Dark Brown Chernozemic soil columns. The δa15N of nitrate-N in the zones of the high nitrate-N accumulation was lower than that of the soil derived nitrate-N but not necessarily lower than the δa15N of fertilizer material as was the case in previously reported field expts. Calcn. of the fate of the fertilizer N based on the principle of isotopic dilution provided semiquant. ests. of the added N found in the plant, the soil, and the leachate.

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=> d his

     (FILE 'HOME' ENTERED AT 13:55:08 ON 13 APR 2005)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 13:55:36 ON 13 APR 2005
L1           17 S "CARK"
L2         1949 S "CARDIAC-RELATED"
L3         4025 S ANKYRIN(2W)REPEAT
L4            4 S L2 AND L3
L5            3 DUP REM L4 (1 DUPLICATE REMOVED)
L6           15 DUP REM L1 (2 DUPLICATES REMOVED)

=> s modulator? or inhibit? or activat? or stimulat?
   3 FILES SEARCHED...
L7     11583440 MODULATOR? OR INHIBIT? OR ACTIVAT? OR STIMULAT?

=> s cardiac (2w) related
L8         4037 CARDIAC (2W) RELATED
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=> s l8 and ankyrin
L9            4 L8 AND ANKYRIN

=> s l3 and l7
L10        2200 L3 AND L7

=> s human and l10
L11        1035 HUMAN AND L10

=> s cardiac and l11
L12          87 CARDIAC AND L11

=> dup rem l12
PROCESSING COMPLETED FOR L12
L13           40 DUP REM L12 (47 DUPLICATES REMOVED)

=> d 1-40 ibib ab

L13  ANSWER 1 OF 40  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:158822  HCAPLUS
DOCUMENT NUMBER:          142:259417
TITLE:                    Methods for identifying risk of melanoma by
                          genome-wide SNP scanning proximal to susceptibility
                          loci NRP1, NID2, ENDO180, CDK10, FPGT, CARK, PCLO, and
                          REPS2 and treatments thereof
INVENTOR(S):              Roth, Richard B.; Nelson, Matthew Roberts; Kammerer,
                          Stefan M.; Braun, Andreas; Hoyal-Wrightson, Carolyn R.
PATENT ASSIGNEE(S):       Sequenom, Inc., USA
SOURCE:                   PCT Int. Appl., 418 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   4
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.          DATE
     ---------------     ----   --------    --------------------     --------
     WO 2005017176        A2    20050224    WO 2004-US14238          20040505
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
             SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
             SN, TD, TG
     US 2005064440        A1    20050324    US 2003-703789           20031106
PRIORITY APPLN. INFO.:                      US 2003-489703P       P  20030723
                                            US 2003-703789        A  20031106
                                            US 2003-703817        A  20031106
                                            US 2003-704513        A  20031106
                                            US 2002-424475P       P  20021106
AB    Provided herein are methods for identifying risk of melanoma in a subject
      and/or subjects at risk of melanoma, reagents and kits for carrying out
      the methods, methods for identifying candidate therapeutics for treating
      melanoma, therapeutic methods for treating melanoma in a subject and
      compns. comprising one or more melanoma cells and one or more NRP1, NID2,
      ENDO180, CDK10, FPGT, CARK, PCLO or REPS2 directed agents.  The above
      melanoma susceptibility loci: NRP1 (neuropilin 1, also known as NRP,
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VEGF165R (Vascular Endothelial Growth Factor-165 Receptor)), NID2 (Nidogen 2, also known as osteonidogen), ENDO180 (also known UPARAP (urokinase plasminogen **activator** receptor-associated protein), KIAA0709, MRC2 (mannose receptor, C type 2), endocytic receptor (macrophage mannose receptor family)), CDK10 (cyclin-dependent kinase (CDC2-like) 10, also known as cyclin-dependent kinase 10 isoform 1), FPGT (fucose-1-phosphate guanylyltransferase, also known as GFPP and GDP-beta-L-fucose pyrophosphorylase), CARK (**cardiac ankyrin repeat** kinase, near FPGT locus), PCLO (also known as piccolo (presynaptic cytomatrix protein), ACZ, KIAA0559 and aczonin) and REPS2 (RALBP1 associated EPS domain containing 2, also known as POB1 and partner of Ral-binding protein 1) are identified by SNP genome scanning. These embodiments are based upon an anal. of polymorphic variations in loci: NRPI (total 95 polymorphic variants), NID2 (NA), ENDO180 (43), CDK10 (103), FPGT and nearby CARK (92), PCLO (76) or REPS2 (103) nucleic acid, exemplified by nucleotide sequences of SEQ ID NO: 1-17. Specifically provided are a series of SNP markers, in particular, ENDO180 A16727 (A at position 16727, SEQ ID NO: 3), CDK10 G36589 and T44544 and G48304 (SEQ ID NO: 4), FPGT G206 and A9261 T37592 (SEQ ID NO: 5), PCLO G53843 and G63624 and A65039 (SEQ ID NO: 6), or REPS2 G10537 and C25216 and T119368 (SEQ ID NO: 7). Also provided are compns. comprising a melanoma cell and/or a NRPI, NID2, ENDO180, CDK10, FPGT, CARK, PCLO or REPS2 nucleic acid, or a fragment or substantially identical nucleic acid thereof, with a RNAi, siRNA, a complementary or antisense DNA or RNA, or ribozyme nucleic acid designed from above loci.

L13 ANSWER 2 OF 40 HCAPLUS

ACCESSION NUMBER: 2005:71066 HCAPLUS
DOCUMENT NUMBER: 142:170050
TITLE: DEF domain-containing members of the MAP kinase pathway and their use in screening for drug **inhibitors**
INVENTOR(S): Blenis, John; Murphy, Leon O.
PATENT ASSIGNEE(S): President and Fellows of Harvard College, USA
SOURCE: PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005007090	A2	20050127	WO 2004-US21514	20040702

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-484761P P 20030703

AB Mitogen-**activated** protein (MAP) kinases (e.g., ERK1/2) phosphorylate a variety of target proteins including, for example, several immediate-early gene products (e.g., Fos, Myc, and Jun family proteins). Certain phosphorylation reactions require binding of the MAP kinase to the DEF domain of the target protein. **Inhibitors** that block this interaction may be useful therapeutics for **human** disease,

including as antineoplastic agents. This invention provides several advantages over known therapies that directly target the MAP kinase signaling cascade. Typically, most compds. that **inhibit** the MAP kinase pathway are non-specific and **inhibit** more than one enzyme, and the targeted **inhibited** kinases are not available to perform normal physiol. functions necessary for cell survival, whereas therapeutic methods of the present invention **inhibit** the **activation** of particular target proteins and leave the MAP kinases enzymically active and available to phosphorylate other non-DEF domain-containing proteins. Thus, DEF domains are identified in a large number of proteins, and the principles of the invention are exemplified using the immediate-early gene, c-Fos. Screening assays useful for identifying compds. that **inhibit** the MAP kinase-DEF domain interaction are also disclosed.

L13 ANSWER 3 OF 40 HCAPLUS

ACCESSION NUMBER: 2005:15932 HCAPLUS
DOCUMENT NUMBER: 142:108526
TITLE: Sequences upstream of the CARP (**cardiac ankyrin repeat**) protein gene, vectors containing them and uses thereof
INVENTOR(S): Benoit, Patrick; Schwartz, Bertrand; Branellec, Didier; Chien, Kenneth R.; Chen, Ju
PATENT ASSIGNEE(S): Fr.
SOURCE: U.S. Pat. Appl. Publ., 54 pp., Cont.-in-part of U.S. Ser. No. 5,337.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005004058	A1	20050106	US 2004-802030		20040317
US 2003039984	A1	20030227	US 2001-5337		20011207
PRIORITY APPLN. INFO.:			US 2000-251582P	P	20001207
			US 2001-5337	A2	20011207

AB The invention relates to promoter sequences derived from a portion upstream of the coding sequence of the gene for the CARP protein (**Cardiac Ankyrin Repeat** Protein), and which are capable of controlling the level and the specificity of expression of a transgene in vivo in **cardiac** muscle cells. The invention thus claims compns., constructs, vectors and their uses in vivo for the transfer and expression of a nucleic acid in vivo in **cardiac** muscle cells. The subject of the present invention is also the use of the promoter sequences for generating transgenic animals which constitute models for studying certain **cardiac** pathologies. A deletion series of the **human** CARP gene promoter was constructed in combination with different cis-regulatory elements and tested for transcriptional activity with a luciferase reporter in cardiomyocyte cell cultures. A truncated -1543 CARP promoter and a **human** **cardiac** α-actin 5'-UTR clone had higher transcriptional activity than other constructs and was not expressed in MDCK epithelial cells. The **cardiac**-specific expression using the CARP promoter was higher and more specific compared to muscle expression than constructs that used an α-actin promoter or a gene SM22 promoter.

L13 ANSWER 4 OF 40 HCAPLUS

ACCESSION NUMBER: 2004:838610 HCAPLUS
DOCUMENT NUMBER: 141:312238
TITLE: DNA microarray analysis of gene expression in the

diagnosis of estrogen receptor positive- and negative-breast cancer

INVENTOR(S): Erlander, Mark G.; Ma, Xiao-Jun; Wang, Wei; Wittliff, James L.
PATENT ASSIGNEE(S): Arcturus Bioscience, Inc., USA
SOURCE: PCT Int. Appl., 226 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004079014	A2	20040916	WO 2002-XA2004006736	20040304

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, CN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004079014	A2	20040916	WO 2004-US6736	20040304

W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-451942P P 20030304
WO 2004-US6736 A 20040304

AB The invention relates to the identification and use of gene expression profiles, or patterns, suitable for identification of populations that are pos. and neg. for estrogen receptor expression. The gene expression profiles may be embodied in nucleic acid expression, protein expression, or other expression formats, and may be used in the study and/or diagnosis of cells and tissue in breast cancer as well as for the study and/or determination of prognosis of a patient, including breast cancer survival.

L13 ANSWER 5 OF 40 EMBASE on STN

ACCESSION NUMBER: 2004396295 EMBASE
TITLE: Gene transfer in tissue repair: Status, challenges and future directions.
AUTHOR: Eming S.A.; Krieg T.; Davidson J.M.
CORPORATE SOURCE: S.A. Eming, Department of Dermatology, University of Cologne, Joseph-Stelzmann Str. 9, 50931 Koln, Germany. sabine.eming@uni-koeln.de
SOURCE: Expert Opinion on Biological Therapy, (2004) Vol. 4, No. 9, pp. 1373-1386.
Refs: 129

ISSN: 1471-2598 CODEN: EOBTA2
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 022 Human Genetics
027 Biophysics, Bioengineering and Medical Instrumentation
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20041007
Last Updated on STN: 20041007

AB Wound repair involves a complex interaction of various cell types, extracellular matrix molecules and soluble mediators. Details on signals controlling wound cell activities are beginning to emerge. In recent years this knowledge has been applied to a number of therapeutic strategies in soft tissue repair. Key challenges include re-adjusting the adult repair process in order to augment diseased healing processes, and providing the basis for a regenerative rather than a reparative wound environment. In particular, the local delivery of pluripotent growth factor molecules to the injured tissue has been intensively investigated over the past decade. Limited success of clinical trials indicates that an important aspect of the growth factor wound-healing paradigm is the effective delivery of these polypeptides to the wound site. A molecular genetic approach in which genetically modified cells synthesise and deliver the desired growth factor in a time-regulated manner is a powerful means to overcome the limitations associated with the (topical) application of recombinant growth factor proteins. This article summarises repair mechanisms and their failure, and gives an overview of techniques and studies applied to gene transfer in tissue repair. It also provides perspectives on potential targets for gene transfer technology.

L13 ANSWER 6 OF 40 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:46913 SCISEARCH
THE GENUINE ARTICLE: 760BR
TITLE: Rapid muscle-specific gene expression changes after a single bout of eccentric contractions in the mouse
AUTHOR: Barash I A; Mathew L; Ryan A F; Chen J; Lieber R L (Reprint)
CORPORATE SOURCE: VA Med Ctr, Dept Orthopaed 9151, 3350 La Jolla Village Dr, La Jolla, CA 92161 USA (Reprint); Univ Calif San Diego, Dept Orthopaed, La Jolla, CA 92093 USA; Univ Calif San Diego, Dept Bioengn, La Jolla, CA 92093 USA; Univ Calif San Diego, Dept Surg, La Jolla, CA 92093 USA; Univ Calif San Diego, Biomed Sci Grad Grp, La Jolla, CA 92093 USA; Dept Vet Affairs Med Ctr, San Diego, CA 92161 USA
COUNTRY OF AUTHOR: USA
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY-CELL PHYSIOLOGY, (1 FEB 2004) Vol. 286, No. 2, pp. C355-C364.
Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
ISSN: 0363-6143.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 92
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Eccentric contractions (ECs), in which a muscle is forced to lengthen while **activated**, result in muscle injury and, eventually, muscle strengthening and prevention of further injury. Although the mechanical basis of EC-induced injury has been studied in detail, the biological response of muscle is less well characterized. This study presents the development of a minimally invasive model of EC injury in the mouse,

follows the time course of torque recovery after an injurious bout of ECs, and uses Affymetrix microarrays to compare the gene expression profile 48 h after ECs to both isometrically **stimulated** muscles and contralateral muscles. Torque dropped by similar to55% immediately after the exercise bout and recovered to initial levels 7 days later. Thirty-six known genes were upregulated after ECs compared with contralateral and isometrically **stimulated** muscles, including five muscle-specific genes: muscle LIM protein (MLP), muscle **ankyrin repeat** proteins (MARP1 and -2; also known as **cardiac ankyrin repeat** protein and Arpp/Ankrd2, respectively), Xin, and myosin binding protein H. The time courses of MLP and MARP expression after the injury bout (determined by quantitative real-time polymerase chain reaction) indicate that these genes are rapidly induced, reaching a peak expression level of 6-11 times contralateral values 12-24 h after the EC bout and returning to baseline within 72 h. Very little gene induction was seen after either isometric **activation** or passive stretch, indicating that the MLP and MARP genes may play an important and specific role in the biological response of muscle to EC-induced injury.

L13 ANSWER 7 OF 40 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER:	2004:500197 SCISEARCH
THE GENUINE ARTICLE:	822SZ
TITLE:	The Ankrd2 protein, a link between the sarcomere and the nucleus in skeletal muscle
AUTHOR:	Kojic S; Medeot E; Guccione E; Krmac H; Zara I; Martinelli V; Valle G; Faulkner G (Reprint)
CORPORATE SOURCE:	Int Ctr Genet Engn & Biotechnol, Padriciano 99, I-34012 Trieste, Italy (Reprint); Int Ctr Genet Engn & Biotechnol, I-34012 Trieste, Italy; Univ Padua, CRIBI, I-35121 Padua, Italy
COUNTRY OF AUTHOR:	Italy
SOURCE:	JOURNAL OF MOLECULAR BIOLOGY, (28 MAY 2004) Vol. 339, No. 2, pp. 313-325. Publisher: ACADEMIC PRESS LTD ELSEVIER SCIENCE LTD, 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND. ISSN: 0022-2836.
DOCUMENT TYPE:	Article; Journal
LANGUAGE:	English
REFERENCE COUNT:	60

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Ankrd2 may be a link between the sarcomere and the nucleus; a similar role has recently been proposed for CARP that has a high level of structural and functional conservation with Ankrd2. Both Ankrd2 and CARP are involved in striated muscle hypertrophy. The mechanism by which muscle stretch is sensed and signals are transduced is still unknown; however, Ankrd2 and CARP could play similar roles in pathways leading to hypertrophy, the triggering mechanisms being heart pressure overload monitored by CARP and mechanical stretch in skeletal muscle monitored by Ankrd2. Recently Ankrd2 and CARP have been proposed as members of a family of muscle **ankyrin repeat** proteins (MARPs) that form a complex with titin, myopalladin and calpain protease p94, involved in signaling and regulation of gene expression in response to muscle stress. Here, we show that Ankrd2 is able to interact with the Z-disc protein telethonin as well as being able to interact with three transcription factors: YB-1, PML and p53. Ankrd2 binding to the ubiquitous transcription factor YB-1 can be demonstrated both in vitro and in vivo; this is not very surprising, since a similar interaction was previously described for CARP. However, the interactions with PML and p53 are unexpected new findings, with interesting implications in the Ankrd2 signaling cascade. Ankrd2 co-localizes with the transcriptional co-**activator** and co-repressor PML in nuclear bodies (NBs) in **human** myoblasts as detected by confocal immunofluorescence. Interestingly, we show that

Ankrd2 not only binds the tumor suppressor protein p53 both in vitro and in vivo but also enhances the up-regulation of the p21(WAFI/CIPI) promoter by p53. Therefore, our findings strengthen the hypothesis that Ankrd2 may be involved in sensing stress signals and linking these to muscle gene regulation.

L13 ANSWER 8 OF 40 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004324551 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15133065
TITLE: Maternal nutrient restriction alters gene expression in the ovine fetal heart.
AUTHOR: Han Hyung-Chul; Austin Kathleen J; Nathanielsz Peter W; Ford Stephen P; Nijland Mark J; Hansen Thomas R
CORPORATE SOURCE: Center for the Study of Fetal Programming and Department of Animal Science, University of Wyoming, Laramie, WY 82071, USA.
CONTRACT NUMBER: 1P20RR16474-01 (NCRR)
HD21350 (NICHD)
SOURCE: Journal of physiology, (2004 Jul 1) 558 (Pt 1) 111-21.
Electronic Publication: 2004-05-07.
Journal code: 0266262. ISSN: 0022-3751.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200501
ENTRY DATE: Entered STN: 20040701
Last Updated on STN: 20050120
Entered Medline: 20050119

AB Adequate maternal nutrient supply is critical for normal fetal organogenesis. We previously demonstrated that a global 50% nutrient restriction during the first half of gestation causes compensatory growth of both the left and right ventricles of the fetal heart by day 78 of gestation. Thus, it was hypothesized that maternal nutrient restriction significantly altered gene expression in the fetal **cardiac** left ventricle (LV). Pregnant ewes were randomly grouped into control (100% national research council (NRC) requirements) or nutrient-restricted groups (50% NRC requirements) from day 28 to day 78 of gestation, at which time fetal LV were collected. Fetal LV mRNA was used to construct a suppression subtraction cDNA library from which 11 cDNA clones were found by differential dot blot hybridization and virtual Northern analysis to be up-regulated by maternal nutrient restriction: caveolin, stathmin, G-1 cyclin, alpha-actin, titin, **cardiac ankyrin repeat** protein (CARP), **cardiac**-specific RNA-helicase **activated** by MEF2C (CHAMP), endothelial and smooth muscle derived neuropilin (ESDN), prostatic binding protein, NADH dehydrogenase subunit 2, and an unknown protein. Six of these clones (**cardiac** alpha-actin, cyclin G1, stathmin, NADH dehydrogenase subunit 2, titin and prostatic binding protein) have been linked to **cardiac** hypertrophy in other species including **humans**. Of the remaining clones, caveolin, CARP and CHAMP have been shown to **inhibit** remodelling of hypertrophic tissue. Compensatory growth of fetal LV in response to maternal undernutrition is concluded to be associated with increased transcription of genes related to **cardiac** hypertrophy, compensatory growth or remodelling. Counter-regulatory gene transcription may be increased, in part, as a response to moderating the degree of **cardiac** remodelling. The short- and long-term consequences of these changes in fetal heart gene expression and induction of specific homeostatic mechanisms in response to maternal undernutrition remain to be determined.

L13 ANSWER 9 OF 40 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:122239 BIOSIS

DOCUMENT NUMBER: PREV200400126246
TITLE: Molecular mechanisms underlying RyR2 (Ca2+ release channel) dysfunction in stress-induced VT.
AUTHOR(S): Thomas, Lowri [Reprint Author]; George, Christopher [Reprint Author]; Lai, F. Anthony [Reprint Author]
CORPORATE SOURCE: Wales Heart Research Institute, UWCM, Cardiff, UK
SOURCE: Biophysical Journal, (January 2004) Vol. 86, No. 1, pp. 49a. print.
Meeting Info.: 48th Annual Meeting of the Biophysical Society. Baltimore, MD, USA. February 14-18, 2004. Biophysical Society.
ISSN: 0006-3495 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Mar 2004
Last Updated on STN: 3 Mar 2004
AB Excitation-contraction coupling in **cardiac** muscle is underpinned by Ca2+ release from the sarcoplasmic reticulum (SR) via the ryanodine receptor isoform 2 (RyR2). Point mutations in the gene encoding RyR2 are associated with stress-induced ventricular tachycardia (VT), a rare disorder frequently linked with abnormal intracellular Ca2+ handling which may result in sudden death. GFP-tagged **human** RyR2 containing VT-associated mutations in the N-terminus and central domain (L433P and N2386I, respectively) have been generated and expressed in a **human** embryonic kidney (HEK) cell model. Resting (Ca2+) and caffeine-**activated** Ca2+ release was analysed in HEK cells expressing either wild-type (WT) or mutant channels using confocal microscopy. Homotetrameric N2386I mutant channels exhibited augmented Ca2+ release and enhanced sensitivity to caffeine **activation** when compared with WT RyR2. In contrast, Ca2+ release via channels formed from RyR2 L433P exhibited a right-shifted dose response to caffeine **activation**, although at maximal caffeine **activation** (>5mM) Ca2+ release was similar to that determined in cells expressing WT RyR2. We investigated whether these mutations disrupted RyR2 interaction with accessory proteins involved in normal channel regulation. cDNA cassettes encompassing WT or mutant sequences (NI, 2320-2406aa; LP, 400-473aa) were constructed and screened against a **human cardiac** cDNA library using a yeast two hybrid system. The N2386I mutation abolished association with phosphoprotein enriched in diabetes (PED) and **cardiac ankyrin repeat** protein (CARP), which occurred with the corresponding WT domain. L433P and its corresponding WT domain did not physically interact with accessory proteins. These results demonstrate that RyR2 mutations linked with stress-induced VT alter channel **activation**. Our approach may represent a powerful framework to investigate the molecular basis of abnormal RyR2 function as a causative mechanism in the pathogenesis of stress-induced VT.

ACCESSION NUMBER: 2004:7716 HCAPLUS
DOCUMENT NUMBER: 140:248041
TITLE: A functional genomics approach for the identification of putative tumor suppressor genes: Dickkopf-1 as suppressor of HeLa cell transformation
AUTHOR(S): Mikheev, Andrei M.; Mikheeva, Svetlana A.; Liu, Binrong; Cohen, Pinchas; Zarbl, Helmut
CORPORATE SOURCE: Division of Public Health, Program in Cancer Biology, Fred Hutchinson Cancer Research Center Seattle, WA, 98104-2092, USA
SOURCE: Carcinogenesis (2004), 25(1), 47-59
CODEN: CRNGDP; ISSN: 0143-3334
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal

LANGUAGE: English

AB We described previously the isolation and characterization of two non-tumorigenic revertants from the HeLa cervical carcinoma cell line, and demonstrated that loss of the transformed phenotype in these cells was the result of dominant somatic mutations. The goal of the present study was to use cDNA microarrays to identify candidate tumor suppressors among the set of genes whose increased expression correlated with loss of tumorigenicity in both revertants. Among the genes with significantly increased expression levels in both HA and HF revertants we identified Insulin Growth Factor Binding Protein-3 (IGFBP-3) and the Dickkopf-1 (DKK-1) genes. Both of these genes encode secreted proteins implicated in the modulation cell growth and differentiation, and IGFBP-3 was shown previously to have tumor suppressing activity. To test the hypothesis that increased expression of IGFBP-3 or the DKK-1 genes could have contributed to the suppression of tumorigenicity in the revertants, we expressed IGFBP-3 or DKK-1 in HeLa cells, and assessed their effects on anchorage dependent and independent growth, and tumor formation in athymic nude mice. Ectopic expression of IGFBP-3 or DKK-1 resulted in significantly decreased growth in soft agar. HeLa cells expressing ectopic IGFBP-3 or DKK-1 showed statistically significant differences in the kinetics of tumor formation. In any tumors that arose in animals injected with the IGFBP-3 expressing cells, there was a complete loss of IGFBP-3 activity, as measured by binding to IGF-1 and IGF-2 proteins. All tumors that arose after injection of cells expressing DKK-1, invariably showed almost a complete loss of ectopic DKK-1 expression. The observations that loss of DKK-1 expression or IGFBP-3 activity was required for tumorigenicity suggested that both proteins encode putative tumor suppressor genes. We also show that while DKK-1 expression does not affect cell growth in vitro, the protein does sensitize cells to apoptosis. We also demonstrated that effect of DKK-1 was not due to **inhibition** of β-catenin/TCF4-regulated transcription. Taken together, our results indicate that somatic cell genetics combining with gene expression profiling may be a useful approach for the identification of functional suppressors of malignant cell growth.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 11 OF 40 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
DUPLICATE 2

ACCESSION NUMBER: 2003-25244 BIOTECHDS

TITLE: Identifying biomarker genes using nucleic acid microarrays, useful for molecular diagnostic and pathology applications, comprises comparing the Gibbs-likelihood ratios for each gene and determining a rank order for the gene;
cell type biomarker identification using DNA array for use in disease diagnosis

AUTHOR: DOOLEY T P; CURTO E V; DAVIS R L

PATENT ASSIGNEE: INTEGRIDERM INC

PATENT INFO: WO 2003067217 14 Aug 2003

APPLICATION INFO: WO 2003-US3673 10 Feb 2003

PRIORITY INFO: US 2002-354519 8 Feb 2002; US 2002-354519 8 Feb 2002

DOCUMENT TYPE: Patent

LANGUAGE: English

OTHER SOURCE: WPI: 2003-731515 [69]

AB DERWENT ABSTRACT:

NOVELTY - Identifying 1 or more biomarker genes for a type of cells among a group of (m) different cell types, from a multiplicity of genes whose expression levels in cells of the group are measured using nucleic acid arrays, to generate a plurality of measurements of expression levels for the m types of cells, by comparing the likelihood ratios of (m) and (m-1) for each gene and determining a rank order for the gene among the multiplicity, is new.

DETAILED DESCRIPTION - Identifying 1 or more biomarker genes for a

type of cells among a group of (m) different cell types, from a multiplicity of genes whose expression levels in cells of the group are measured using nucleic acid arrays, to generate a plurality of measurements of expression levels for the m types of cells, comprising: (a) calculating, for each gene, a likelihood ratio in the first type of cells by dividing: (i) the product of (m-1) and the measurement for the first type of cells; by (ii) the sum of the measurements for the m types of cells excluding the measurement for the first type of cells; (b) repeating step (a) for (m-1) times to calculate, for the gene, a likelihood ratio in each of the m types of cells excluding the first type of cells, to obtain (m-1) likelihood ratios for the gene; and (c) comparing the likelihood ratio of step (a) with the (m-1) likelihood ratios of step (b) for each gene and determining a rank order for the gene among the multiplicity, where the one or more biomarker genes are identified from the rank order. INDEPENDENT CLAIMS are also included for: (1) a gene which is an up-regulated biomarker of metastatic melanoma cells, primary cutaneous melanoma cells, melanocytes, keratinocytes or fibroblasts; and (2) a sequence selected from genes and sequences listed in the specification, and their combinations, which is a diagnostic biomarker for a mammal.

BIOTECHNOLOGY - Preferred Method: In the above method, a natural logarithm is taken for each likelihood ratio calculated for each gene in each type of cells in the group and the natural logarithm is designated as the Gibbs likelihood for the gene, where the rank order is determined according to the Gibbs likelihood for the gene among the multiplicity. The comparing step further comprises ordering the gene by the Gibbs likelihood, or sum of the Gibbs likelihood for the gene in the m types of cells, or average of the Gibbs likelihood for the gene in the m types of cells, to generate a Gibbs gene expression rank, where the rank order is determining based on the Gibbs gene expression rank. An arithmetic mean of the Gibbs likelihood for the genes in the multiplicity is taken and a standard deviation of the Gibbs likelihood in the m types of cells is assessed, where the Gibbs likelihood for the gene in the first type of cells is represented in the units of the standard deviation plus or minus the corresponding arithmetic mean to determine a rank for the gene in the rank order. One or more genes with a Gibbs likelihood greater than u times the standard deviation are designated as up-regulated biomarker genes of the first type of cells. The u is greater than 1 or equals 2. One or more genes with a Gibbs likelihood ratio smaller than v times the standard deviation are designated as down-regulated biomarker genes of the first type of cells. The v is greater than 1 or equals 2. A median is taken for the likelihood ratios calculated for each gene in the m types of cells, the median being designated as median likelihood, where the rank order is determined according to the median likelihood for the gene among the multiplicity. The comparing further comprises generating a median rank distribution by sorting the genes in the multiplicity according to the corresponding median likelihood, where the rank order is determined based on the median gene expression rank. An arithmetic mean of the median likelihood for the genes in the multiplicity is taken and a standard deviation of the median likelihood in the m types of cells is assessed, where the median likelihood for the gene in the first type of cells is represented in the units of the standard deviation plus or minus the corresponding arithmetic mean to determine a rank for the gene in the rank order. One or more genes with a median likelihood greater than u times the standard deviation are designated as down-regulated biomarker genes of the first type of cells, where u is greater than 1 or equals 2. One or more with a median likelihood ratio smaller than v times the standard deviation are designated as up-regulated biomarker genes of the first type of cells, where v is greater than 1 or equals 2. The m is greater than or equals 3. The different types of cells are cells or tissues that are normal or abnormal. The different types of cells may be exposed to one or more of the treatments selected from treatments with a chemical, a drug, a toxin, a biological agent, an environmental stimulus,

and their combinations. The environmental stimulus comprises electromagnetic radiation, heat, mechanical force, or any of their combinations. The different types of cells are skin cells. The skin cells comprise keratinocyte cells, melanocyte cells, fibroblast cells or their combinations. The skin cells comprise melanocyte cells, cutaneous primary melanoma cells, metastatic melanoma cells, or their combinations. Preferred Gene: The gene that is an up-regulated biomarker of metastatic melanoma cells is selected from a transducer of ERBB2 member 2, Finkel-Biskis-Reilly murine sarcoma virus, RAB6, homeobox A10, Tax1 binding protein 1, SET binding factor 1, maternally expressed 3, ubiquitination factor E4A, solute carrier family 1 member 3, solute carrier family 2 member 4, heterogeneous nuclear ribonucleoprotein A3, hemogen, apolipoprotein D, cartilage linking protein 1, RNA helicase-related protein, hippocalcin, dystrobrevin alpha, coagulation factor C homologue, putative receptor protein, mitochondrial ornithine transporter, cyclin G2, EST cDNA ID 471826, EST cDNA ID 427657, EST cDNA ID 298104, EST cDNA ID 1571632, EST cDNA ID 591143 and EST cDNA ID 208082 listed in the specification. The gene that is an up-regulated biomarker of primary cutaneous melanoma cells is selected from histidyl-tRNA synthetase homologue and an EST cDNA ID 209841 given in the specification. The gene that is an up-regulated biomarker of melanocytes is selected from hypothetical protein expressed in osteoblasts, nidogen 2, erythroid alpha-spectrin 1, afx1 transcription factor, sarcoma-amplified sequence, visinin-like 1, checkpoint suppressor 1, putative nuclear protein, ephrin-B1, biglycan, protein tyrosine phosphatase IVA member 2, prostaglandin E synthase, mitogen-**activated** protein kinase 10, methylenetetrahydrofolate dehydrogenase, mitochondrial F1 alpha 1 ATP synthase, peroxisomal biogenesis factor 12, pleiomorphic adenoma gene 1, HLA class II region expressed gene K4, coagulation factor VIII-associated, and **cardiac** muscle slow twitch 2 ATPase. Alternatively, the gene is selected from galectin 3, syndecan binding protein (syntenin), dystroglycan 1, prostate differentiation factor, glutaminyl cyclotransferase, Na+/K+ transporting ATPase alpha 1, cAMP-dependent protein kinase I alpha 1, protein tyrosine phosphatase IVA2, fyn oncogene, 6-pyruvoyl-tetrahydropterin synthas e, dihydropyrimidinase, pirin, major histocompatibility complex I-C, 4F2 antigen heavy chain (solute carrier 3), abl-interactor 2b, coxsackie virus and adenovirus receptor, prostatic binding protein, proteolipid protein 1, v-abl oncogene 1, ets2 repressor factor, proline-rich Gla 1, axin 1 up-regulated, voltage-gated K+ channel beta subunit, vaccinia-related kinase 3, EST cDNA ID 712604, EST cDNA ID 267859, EST cDNA ID 320588, and EST cDNA ID 305843 listed in the specification. The gene that is an up-regulated biomarker gene for melanocytes is also selected from ribosomal protein L30 and orosomucoid 1. The gene that is a down-regulated biomarker gene for metastatic melanoma cells is selected from keratin 1, fibroblast growth factor 12, intercellular adhesion molecule 2, hematopoietic protein 1, nuclear domain 10, interleukin-1 receptor-associated kinase, and macrophage associated antigen. The gene that is an up-regulated biomarker for keratinocytes is selected from small proline-rich protein 2C, type VIII alpha I collagen, type IV alpha 4 collagen, trophinin, chondroitin sulfate proteoglycan 3, activin A receptor type II-like 1, paired box gene 6, homeobox D4, homeobox B5, zinc finger protein 131, special AT-rich sequence binding 1, ubiquitin specific protease 16, pyrolin-5-carboxylate synthetase, neural expressed developmentally down-regulated 5, ribonuclease P (30kD), protein tyrosine phosphatase (rec F), endothelial lipase, ras homologue gene, valyl-tRNA synthetase 2, arylsulfatase A, aldo-keto reductase 1C1, protein phosphatase 1 regulatory 3C, developmentally regulated GTP-binding 1,3-hydroxybutyrate dehydrogenase, adipose most abundant transcript, pancreatic polypeptide 2, solute carrier 11 A2, solute carrier 22A11, **cardiac ankyrin repeat** protein, heparin binding growth factor binding protein, Ewing sarcoma break point region

1, and EST cDNA ID 415281, EST cDNA ID 460258, EST cDNA ID 415235, EST cDNA ID 67330, EST cDNA ID 460247, EST cDNA ID 1522679, EST cDNA ID 378420, EST cDNA ID 341317, EST cDNA ID 461287, and EST cDNA ID 415613 listed in the specification. The gene that is an up-regulated biomarker for fibroblasts is selected from fibulin 5, interleukin 2 receptor gamma, eukaryotic translation elongation factor 2, mitochondrial ribosomal protein L23, ribosomal protein L7a, SEC23-like protein B, solute carrier family 16A3, metallothionein IF, metallothionein IH, interferon induced transmembrane 2, Dickkopf homologue 3, episialin, high mobility group protein I-C, and growth factor receptor-bound protein 14, EST cDNA ID 1049033, and EST cDNA ID 378458 listed in the specification. The gene that is a down-regulated biomarker gene for keratinocytes is selected from MIC2 (antigen to antibodies 12E7, F21 and O13), microtubule-associated protein 1B, monocytic leukemia zinc finger protein, Clathrin heavy chain 1, non-metastatic cells 4, TC 10-like Rho GTPase, Myelin gene expression factor 2, and CAAX box 1, EST cDNA ID 53371, and EST cDNA ID 1467936 listed in the specification. The gene that is a down-regulated biomarker gene for fibroblasts is selected from long chain 2 of Fatty-acid coenzyme A ligase, calcium modulating ligand and nuclear receptor coactivator 3 (amplified breast cancer-AIBI). Preferred Sequence: The sequence is a molecular target for therapeutics of a mammalian disorder or for the discovery of therapeutics of a mammalian disorder. The mammal is a **human** and the mammalian disorder is a **human** disorder.

USE - The method is useful in identifying biomarkers using nucleic acid microarrays. The biomarkers of skin may be used in molecular diagnostic and pathology applications in normal and abnormal tissues and cell. The biomarker genes may also be used as molecular targets for therapeutics of a disorder or a disease in **humans**.(27 pages)

L13 ANSWER 12 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:532691 HCAPLUS
DOCUMENT NUMBER: 139:95435
TITLE: Modified receptors on cell membranes for the discovery of therapeutic ligands
INVENTOR(S): Schwartz, Thue W.; Martini, Lene; Heydorn, Arne; Jorgensen, Rasmus
PATENT ASSIGNEE(S): 7TM Pharma A/S, Den.
SOURCE: PCT Int. Appl., 122 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003055914	A2	20030710	WO 2002-DK900	20021220
WO 2003055914	A3	20031023		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

DK 2001-1944	A	20011221
DK 2002-113	A	20020122
DK 2002-1043	A	20020703
US 2002-394122P	P	20020703

AB A drug discovery method is provided for selecting a compound selected from the group consisting of a small organic substance, a biopharmaceutical, or an antibody or part thereof. The method comprises the steps of (i) expressing one or more receptors on a cell membrane, such as, e.g., an exterior cell surface of a cell, (ii) contacting one or more expressed receptors with a test compound or a selection of test compds. (libraries), and (iii) selecting one or more compds. based on its ability to bind one or more receptors. The step of expressing the one or more receptors comprises capturing one or more receptors on the exterior cell surface in a conformation that predominantly enables binding or interaction with a ligand, and the conformation that predominantly enables binding or interaction with a ligand is provided by modification of one or more receptors by a method comprising at least one of the following: (a) fusion with any protein which keeps the receptor in the desired conformation such as, e.g. an arrestin, a modified arrestin, a G-protein or a modified G-protein, (b) site-directed mutagenesis, and (c) deletion. The receptors may be captured on the exterior cell surface by at least one of the following: (d) interaction of the receptor with a scaffolding protein, optionally, with a scaffolding protein network and (e) means for blocking receptor internalization, e.g. by co-expression of a mutated dynamin or a modified arrestin or by use of chems. such as, e.g., sucrose and/or Tris. Thus, by coexpressing of either the wild-type receptor or by modifying the receptor by engineering for example a recognition motif for a strong binder into its structure (for example, a PDZ recognition motif at its C-terminal end), and coexpression of this with a scaffolding protein such as PSD-95 or a modified scaffolding protein which interacts with the cytoskeleton at the cell surface or is made to be closely associated with the membrane through a lipid anchor, a high level of surface expression can be ensured, which will benefit its use in the drug discovery process. As a result of the strong tendency of the scaffolding proteins to interact with each other, just the cotransfection with one or more appropriate scaffolding proteins or modified scaffolding protein may also lead to the formation of patches with high local concns of the receptor or modified receptor, which will be highly beneficial in the drug discovery process where they are used initially to select binding mols. The method is exemplified by expression of the NK1 receptor in an agonist high-affinity binding form at the surface of transfected cells through fusion with arrestin or the N-terminal fragment of arrestin.

L13 ANSWER 13 OF 40 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:1079473 SCISEARCH
THE GENUINE ARTICLE: 750PF
TITLE: Molecular responses of **human** muscle to eccentric exercise
AUTHOR: Chen Y W; Hubal M J; Hoffman E P; Thompson P D; Clarkson P M (Reprint)
CORPORATE SOURCE: Univ Massachusetts, Dept Exercise Sci, 110 Totman Bldg, Amherst, MA 01003 USA (Reprint); Univ Massachusetts, Dept Exercise Sci, Amherst, MA 01003 USA; Childrens Natl Med Ctr, Ctr Genet Med, Washington, DC 20010 USA; George Washington Univ, Washington, DC 20010 USA; Hartford Hosp, Dept Prevent Cardiol, Hartford, CT 06102 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF APPLIED PHYSIOLOGY, (DEC 2003) Vol. 95, No. 6, pp. 2485-2494.
Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
ISSN: 8750-7587.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English

REFERENCE COUNT: 61

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We examined the effect of eccentric exercise on the transcriptome of skeletal muscle in three male **human** volunteers who performed 300 concentric contractions with one leg and 300 eccentric contractions with the opposite leg. Vastus lateralis muscle biopsies were taken from both legs at 4-8 h after exercise, and expression was profiled by using 12,000 gene Affymetrix U95Av2 microarrays. We found a high concordance of expression responses to eccentric contractions between our **human** and rat data from a previous study (Chen YW, Nader GA, Baar KR, Fedele MJ, Hoffman EP, and Esser KA. J Physiol 545: 27-41, 2002) (similar to50% of gene expression changes shared between species). Potential **human** -specific changes included greater inflammatory responses [chemokine (C-C motif) ligand 2, C/EBP delta, and IL-1 receptor] and vascular remodeling (tenascin C and lipocortin II). Induction of c-fos and lipocortin II were confirmed at the protein level, with c-fos localized to myofiber nuclei and lipocortin II to intramuscular capillaries. We also confirmed the eccentric-induced expression of six transcripts by quantitative RT-PCR (**cardiac** ankyrin-repeated protein, chemokine ligand 2, CCAAT/enhancer binding protein delta, IL-1 receptor, tenascin C, and cysteine-rich angiogenic inducer 61). These data provide the first characterization of the transcriptional response of skeletal muscle to eccentric exercise in **humans** and represent a preliminary step in understanding the molecular processes underlying muscle remodeling (including a new focus on rapid changes in the capillary bed) and inflammatory responses after damaging lengthening contractions.

L13 ANSWER 14 OF 40 MEDLINE on STN DUPLICATE 3

ACCESSION NUMBER: 2003492339 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14499857
TITLE: Beta-adrenergic **stimulation** induces **cardiac ankyrin repeat** protein expression: involvement of protein kinase A and calmodulin-dependent kinase.
COMMENT: Comment in: Cardiovasc Res. 2003 Sep 1;59(3):529-31. PubMed ID: 14499851
AUTHOR: Zolk Oliver; Marx Michael; Jackel Elmar; El-Armouche Ali; Eschenhagen Thomas
CORPORATE SOURCE: Institut fur Experimentelle und Klinische Pharmakologie und Toxikologie, Friedrich-Alexander-Universitat Erlangen-Nurnberg, Fahrstr. 17, 91054 Erlangen, Germany.. zolk@pharmakologie.uni-erlangen.de
SOURCE: Cardiovascular research, (2003 Sep 1) 59 (3) 563-72. Journal code: 0077427. ISSN: 0008-6363.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20031023
Last Updated on STN: 20040115
Entered Medline: 20040114

AB OBJECTIVE: The **cardiac ankyrin repeat** protein (CARP), a nuclear transcription co-factor that negatively regulates **cardiac** gene expression, is increased in **human** heart failure and in animal models of **cardiac** hypertrophy. The mechanism by which CARP expression is regulated and the consequences of CARP overexpression on **cardiac** contractility are unknown.
METHODS AND RESULTS: Compared to vehicle treated controls, 4-day treatment of male Wistar rats with the beta-adrenoceptor agonist isoprenaline (2.4 mg/kg per day) induced hypertrophy and significantly increased CARP mRNA and CARP protein levels in left ventricles. The signalling pathways were investigated in more detail in isolated neonatal rat cardiomyocytes.

Treatment of cells with isoprenaline (1 micromol/l) caused a significant increase in CARP mRNA and protein by approximately 50%. Combined beta(1)- and beta(2)-adrenoceptor blockade, **inhibition** of protein kinase A (PKA; Rp-cAMPS, 100 micromol/l), and **inhibition** of calmodulin-dependent protein kinases (CaMK; KN-62, 10 micromol/l) completely reversed the effects of isoprenaline. To examine the consequences of CARP overexpression on contractile function, an adenovirus encoding **human** CARP as well as a control virus were constructed. Although the basal force of contraction was not different, contractile response to Ca(2+) and isoprenaline was significantly diminished in engineered heart tissue infected with the recombinant adenovirus that carries the CARP gene (Ad.CARP). CONCLUSIONS: Our study provides the first evidence that overexpression of CARP, which is thought to act as a transcriptional co-repressor, may deteriorate contractile function of the heart tissue. Furthermore, beta-adrenoceptor **stimulation** and **activation** of PKA and CaMK have been identified as mechanisms that induce expression of CARP in cardiomyocytes.

L13 ANSWER 15 OF 40 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 4

ACCESSION NUMBER: 2003:488346 BIOSIS
DOCUMENT NUMBER: PREV200300490029
TITLE: Gene expression profiling of resting and **activated** vascular smooth muscle cells by serial analysis of gene expression and clustering analysis.
AUTHOR(S): Beauchamp, Nicholas J.; van Achterberg, Tanja A. E.; Engelse, Marten A.; Pannekoek, Hans; de Vries, Carlie J. M. [Reprint Author]
CORPORATE SOURCE: Department of Biochemistry, Academic Medical Center, Meibergdreef 15, K1-163, 1105 AZ, Amsterdam, Netherlands c.j.devries@amc.uva.nl
SOURCE: Genomics, (September 2003) Vol. 82, No. 3, pp. 288-299. print.
ISSN: 0888-7543 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Oct 2003
Last Updated on STN: 22 Oct 2003

AB Migration and proliferation of vascular smooth muscle cells (SMCs) are key events in atherosclerosis. However, little is known about alterations in gene expression upon transition of the quiescent, contractile SMC to the proliferative SMC. We performed serial analysis of gene expression (SAGE) of cultured, **human** SMCs, either grown under resting circumstances or **activated** with an atherogenic stimulus. Analysis of tags, representing 47.209 and 47.259 mRNAs from a library of resting and **activated** SMCs, respectively, identified 105 tags induced and 52 tags repressed greater than fivefold. To evaluate the relevance in SMC biology of unmatched, regulated tags, we performed hierarchical clustering analysis. based on their expression profiles in public SAGE databases, and clustered these novel genes in distinct groups. The regulation in SMCs was confirmed by Northern blotting for representative genes of these groups. Plasminogen **activator inhibitor**-2 has not been associated with atherosclerosis before and was localized to atherosclerotic lesions.

L13 ANSWER 16 OF 40 MEDLINE on STN DUPLICATE 5

ACCESSION NUMBER: 2003017531 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12524226
TITLE: **Cardiac ankyrin repeat** protein (CARP) expression in **human** and murine atherosclerotic lesions: activin induces CARP in smooth muscle cells.
AUTHOR: de Waard Vivian; van Achterberg Tanja A E; Beauchamp

Nicholas J; Pannekoek Hans; de Vries Carlie J M
CORPORATE SOURCE: Department of Biochemistry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.
SOURCE: Arteriosclerosis, thrombosis, and vascular biology, (2003 Jan 1) 23 (1) 64-8.
Journal code: 9505803. ISSN: 1524-4636.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20030114
Last Updated on STN: 20030128
Entered Medline: 20030127
AB OBJECTIVE: **Cardiac ankyrin repeat** protein (CARP) is a transcription factor-related protein that has been studied most extensively in the heart. In the present study, we investigated the expression and the potential function of CARP in **human** and murine atherosclerosis. METHODS AND RESULTS: CARP expression was observed by in situ hybridization in endothelial cells lining **human** atherosclerotic plaques, whereas lesion macrophages were devoid of CARP. Furthermore, we established that CARP mRNA and smooth muscle (SM) alpha-actin antigen both colocalized in a subset of intimal smooth muscle cells (SMCs), whereas no CARP mRNA was encountered in quiescent SMCs in the media. The CARP mRNA-expressing intimal SMCs were distinct from intimal SMCs that synthesized the **activation** marker osteopontin or proliferating cell nuclear antigen. In addition, we showed that activin A, a member of the TGFbeta superfamily that prevents SMC-rich lesion formation, induced CARP mRNA expression in cultured SMCs. CONCLUSIONS: Based on our data and the knowledge that CARP reduces the proliferation of cultured SMCs, we propose that CARP is involved in **inhibition** of vascular lesion formation.

L13 ANSWER 17 OF 40 EMBASE on STN DUPLICATE 6
ACCESSION NUMBER: 2003033741 EMBASE
TITLE: **Cardiac ankyrin repeat** protein (CARP) expression in **human** and murine atherosclerotic lesions: Activin induces carp in smooth muscle cells.
AUTHOR: De Waard V.; Van Achterberg T.A.E.; Beauchamp N.J.; Pannekoek H.; De Vries C.J.M.
CORPORATE SOURCE: Dr. C.J.M. De Vries, Department of Biochemistry, Academic Medical Center, University of Amsterdam, Meibergdreef 15, 1105 AZ Amsterdam, Netherlands. c.j.devries@amc.uva.nl
SOURCE: Arteriosclerosis, Thrombosis, and Vascular Biology, (1 Jan 2003) Vol. 23, No. 1, pp. 64-68.
Refs: 19
ISSN: 1079-5642 CODEN: ATVBFA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20030130
Last Updated on STN: 20030130
AB Objective - **Cardiac ankyrin repeat** protein (CARP) is a transcription factor-related protein that has been studied most extensively in the heart. In the present study, we investigated the expression and the potential function of CARP in **human** and murine atherosclerosis. Methods and Results - CARP expression was observed by in situ hybridization in endothelial cells lining

human atherosclerotic plaques, whereas lesion macrophages were devoid of CARP. Furthermore, we established that CARP mRNA and smooth muscle (SM) α-actin antigen both colocalized in a subset of intimal smooth muscle cells (SMCs), whereas no CARP mRNA was encountered in quiescent SMCs in the media. The CARP mRNA - expressing intimal SMCs were distinct from intimal SMCs that synthesized the **activation** marker osteopontin or proliferating cell nuclear antigen. In addition, we showed that activin A, a member of the TGFβ superfamily that prevents SMC-rich lesion formation, induced CARP mRNA expression in cultured SMCs. Conclusions - Based on our data and the knowledge that CARP reduces the proliferation of cultured SMCs, we propose that CARP is involved in **inhibition** of vascular lesion formation.

L13 ANSWER 18 OF 40 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN DUPLICATE 7

ACCESSION NUMBER: 2002-12430 BIOTECHDS

TITLE: Use of CARP **inhibitors** for treating heart disease; vector-mediated **cardiac**-restricted **ankyrin repeat** protein-**inhibitor** gene transfer and expression in host cell for recombinant protein production and drug screening

AUTHOR: KLUXEN F; HENTSCH B; WILM C; BRAENDLE M; EHRING T; ESCHENHAGEN T; ZOLK O

PATENT ASSIGNEE: MERCK PATENT GMBH

PATENT INFO: WO 2002020003 14 Mar 2002

APPLICATION INFO: WO 2000-EP9324 11 Sep 2000

PRIORITY INFO: EP 2000-119771 11 Sep 2000

DOCUMENT TYPE: Patent

LANGUAGE: English

OTHER SOURCE: WPI: 2002-304316 [34]

AB DERWENT ABSTRACT:

NOVELTY - Use of an **inhibitor** or antagonist of **cardiac** -restricted **ankyrin repeat** protein (CARP) or CARP mRNA to treat heart diseases, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) a composition with at least one of the properties: (a) **inhibition** of CARP protein and/or CARP mRNA; (b) binding to CARP protein and/or CARP mRNA; (c) prevention of CARP from binding to YB-1, or of CARP/YB-1 complex from binding to HF-1a/HF1-b/Mef-2 DNA elements; (d) prevention of CARP protein from down-regulation of **cardiac** ANF or TNC; and (e) enhancement of the expression and/or secretion of ANF from the heart; (2) the use of CARP protein or CARP mRNA/DNA for screening substances which block or **inhibit** CARP or CARP expression; (3) the use of CARP protein or CARP mRNA/DNA as negative regulator of the expression of alpha-myosin heavy chain mRNA; (4) screening an **inhibitor** of CARP protein and/or CARP mRNA, comprising: (a) constructing a first expression vector comprising full-length **human** CARP cDNA together with a stong promoter and a selection marker; (b) constructing a second expression vector comp rising a reporter gene which is under the control of HF-1a/HF-1b/Mef-2 together with a selection marker which is different from that of the first expression vector; (c) transfecting the first and second vectors into a suitable eukaryotic expression cell line; and (d) culturing transfected cells expressing CARP protein as well as the reporter gene product which indicates the CARP activity, together with the **inhibitor** and measuring the reduced activity of the reporter gene product; and (5) the use of CARP or its modifications or variants as a diagnostic means for detecting in vitro heart disorders like heart failure.

ACTIVITY - Cardiant. No biological data is given.

MECHANISM OF ACTION - **Inhibitor** or antagonist of CARP protein or CARP mRNA.

USE - For treating heart disorders, especially heart failure or

heart hypertrophy induced by isoprenalin or phenylephrine.
EXAMPLE - Northern blots were performed using a **human** CARP mRNA. The figure (in arbitrary units) for non-failing hearts was 0.67(0.14, compared to 1.1(0.09 for hearts with idiopathic dilated cardiomyopathy, and 1.1(0.08 for hearts with ischemic cardiomyopathy, showing that CARP mRNA was upregulated in failing hearts.(15 pages)

L13 ANSWER 19 OF 40 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2003-06037 BIOTECHDS
TITLE: Novel purified **ankyrin repeat** domain 2 protein variant or its portion, useful in characterization, diagnosis or treatment of muscle disorder such as muscle hypertrophy and particularly clear cell sarcoma;
recombinant protein production via plasmid expression in host cell use in disease therapy
AUTHOR: WALKER M G
PATENT ASSIGNEE: WALKER M G
PATENT INFO: US 2002127636 12 Sep 2002
APPLICATION INFO: US 2001-758593 10 Jan 2001
PRIORITY INFO: US 2001-758593 10 Jan 2001; US 2001-758593 10 Jan 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2003-039585 [03]
AB DERWENT ABSTRACT:
NOVELTY - A purified **ankyrin repeat** domain 2 protein variant (Ankrd2V) (I) or its portion comprising a sequence (S1) of 329 amino acids fully defined in the specification or an antigenic epitope or biologically active portion of S1, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) an isolated cDNA (II) comprising a nucleic acid sequence encoding (I), where the nucleic acid sequence is selected from a sequence (S2) comprising 1158 base pairs fully defined in the specification or its complement, a fragment of S2 selected from a sequence comprising 576, 253, 569 or 330 base pairs fully defined in the specification or its complement, and a variant of S2 selected from a sequence comprising 255, 275, 315 or 207 base pairs fully defined in the specification or its complement; (2) a composition (III) comprising (II) or its complement and a labeling moiety; (3) a vector (IV) comprising (II); (4) a host cell (V) comprising (IV); (5) a composition (VI) comprising (I) and a pharmaceutically acceptable carrier; and (6) an antibody (VII) produced using (I).
WIDER DISCLOSURE - Also disclosed are: (a) a substrate or probe comprising (II) or its complement; and (b) a transgenic cell line or organism comprising (IV).
ACTIVITY - Cytostatic. No supporting data is given.
MECHANISM OF ACTION - None given.
USE - (I) is useful to screen a number of molecules or compounds to identify at least one ligand, by combining (I) with the molecules or compounds under conditions to allow specific binding, and detecting specific binding, thus identifying a ligand which specifically binds (I), where the molecules or compounds are selected from DNA or RNA molecules, peptide nucleic acids, peptides, proteins, mimetics, agonists, antagonists, antibodies, immunoglobulins, **inhibitors** and drugs.
(I) is useful for preparing and purifying antibodies by immunizing an animal with (I) under conditions to elicit an antibody response, isolating animal antibodies, attaching (I) to a substrate, contacting the substrate with isolated antibodies under conditions to allow specific binding to (I), and dissociating the antibodies from (I), to obtain purified antibodies. (II) is useful to produce a protein by culturing (V) under conditions for protein expression, and recovering the protein from the host cell culture. (II) is useful to detect expression of a nucleic acid in a sample by hybridizing (III) to nucleic acids of the sample, to form hybridization complexes and comparing hybridization complex

formation with a standard, where the comparison indicates expression of the cDNA in the sample, where (III) is attached to a substrate. The method further comprises amplifying the nucleic acids of the sample prior to hybridization. (II) is differentially expressed when compared with the standard and diagnostic of clear cell carcinoma. (II) is useful to screen a number of molecules or compounds, by combining (II) with the molecules or compounds under conditions to allow specific binding, and detecting specific binding, thus identifying a ligand with specifically binds (II), where the molecules or compounds are selected from DNA or RNA molecules, peptide nucleic acids, artificial chromosome constructions, peptides, transcription factor, repressors and regulatory molecules. (VII) is useful for diagnosing conditions or diseases associated with expression of a protein by combining (VII) with a sample to form antibody:protein complexes and comparing complex formation with a standard, where the comparison indicates expression of the protein in the sample, and the expression is diagnostic of clear cell sarcoma (all claimed). (I), (II) or (VII) is useful in the characterization, diagnosis or treatment of muscle disorder such as muscle hypertrophy and particularly clear cell sarcoma. (I) is useful for screening a subject sample for antibodies which specifically bind (I), as potential therapeutics or targets for the identification or development of therapeutics for **cardiac** muscle disorders, or in an assay to identify a clear cell sarcoma or to distinguish between clear cell sarcoma or other muscle cancers. (II) is useful in diagnosis, treatment or prognosis of disorders associated with **cardiac** muscle, or in the evaluation of therapies for such disorders, in assays to distinguish between clear cell sarcoma and other cancers of muscle tissue, for producing transgenic cell lines or organisms which model **human** disorders and upon which potential therapeutic treatments for such disorders may be tested, in hybridization, amplification and screening technologies to identify and distinguish among S2 and related molecule in a sample, to purify a molecule or compound using affinity chromatography methods, or in any molecular biology techniques.

EXAMPLE - A cDNA library was first constructed. The tissue used for muscle library construction was obtained from gluteal muscle tissue removed from a 43-year-old Caucasian female during soft tissue excision, partial ostectomy, and plastic skin repair. The frozen tissue was homogenized and lysed and the lysate was centrifuged. The RNA was extracted isolated and used to construct the cDNA library: pINCY plasmid was then constructed. The plasmid was constructed by digesting the pSPORT1 plasmid with EcoRI restriction enzyme and filling the overhanging ends using Klenow enzyme and 2'-deoxynucleotide 5'-triphosphates (dNTPs). The plasmid was self-ligated and transformed into the bacterial host, Escherichia coli strain JM109. cDNAs were prepared for sequencing and the prepared cDNAs were sequenced. The expression patterns of 16 genes known to function in **cardiac** muscle were compared with the expression patterns of the novel genes with unknown function to determine whether a specified co-expression probability threshold was met. The significance of gene co-expression was evaluated using a probability method to measure a due-to-chance probability of the co-expression set to less than 0.0001, more preferably to less than 0.00001. Through this comparison, **ankyrin repeat** domain 2 protein variant (Ankrd2V) was identified as having a high co-expression probability with the known **cardiac** muscle-associated genes. The cDNAs were extended using the cDNA clone and oligonucleotide primers. Selected cDNA libraries were used as templates to extend the sequence. High fidelity amplification was obtained by polymerase chain reaction (PCR). The extended clones were desalted, concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease and sonicated or sheared prior to religation into pUC18 vector. For shotgun sequences, the digested nucleotide sequences were separated on low concentration agarose gels, fragments were excised, and the agar was digested. Extended clones were religated using T4 DNA ligase into pUC18 vector treated with Pfu DNA

polymerase to fill-in restriction site overhangs, and transfected into E.coli competent cells. Transformed cells were selected on antibiotic-containing media, and individual colonies were picked and cultured overnight at 37degreesC in 384-well plates in Luria Bertani (LB)/2xcarbenicillin liquid media. The cells were lysed, and DNA was amplified using primers, Taq DNA polymerase and Pfu DNA polymerase. Samples were diluted with 20% dimethylsulfoxide (DMSO), and sequenced. (38 pages)

L13 ANSWER 20 OF 40 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2002-17821 BIOTECHDS
TITLE: New polynucleotide encoding the RING finger protein zapop2, useful for diagnosis and treatment of e.g. cancer, also derived protein and antibodies;
recombinant protein production and agonist and antagonist use in disease therapy and gene therapy
AUTHOR: VENEZIA D R; TAFT D W; WHITMORE T E
PATENT ASSIGNEE: VENEZIA D R; TAFT D W; WHITMORE T E
PATENT INFO: US 2002042094 11 Apr 2002
APPLICATION INFO: US 1999-735368 15 Dec 1999
PRIORITY INFO: US 2000-735368 12 Dec 2000
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-488719 [52]
AB DERWENT ABSTRACT:
NOVELTY - Isolated polynucleotide (I) that encodes a polypeptide (II) at least 90% identical with amino acids (aa) 1-599 or 476-599 of a 599 aa protein (2; designated zapop2),as given fully defined in the specification, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) an expression vector (III) comprising the sequence (Ia) encoding complete (2), a promoter and a terminator; (2) a cultured cell (C) containing (III); (3) a DNA construct (DC), encoding a fusion protein (FP), that contains (i) a sequence encoding aa 1-74, 75-376, 476-510 or 555-587 of (2) and (ii), in frame, a sequence encoding another polypeptide; (4) an expression vector (IV) comprising DC, promoter and terminator;(5) cultured cells (V) containing (IV); (6) producing FP by culturing (V); (7) an isolated (II); (8) preparation of (II) by culturing (C); (9) production of antibodies (Ab) by inoculating an animal with (II) or the 1-74, 75-376, 476-510 or 555-587 fragments of (2); (10) Ab prepared this way or any Ab that binds to (II); (11) detecting agonists of zapop2 activity (M1); (12) detecting an abnormality in the zapop2-encoding gene (M2); (13) diagnosing cancer by detecting abnormal levels of zapop2 or the nucleic acid encoding it (M3).

WIDER DISCLOSURE - Also disclosed are orthologous polynucleotides and polypeptides from another species.

BIOTECHNOLOGY - Preferred Nucleic Acid: (I) contains nucleotides 1-1879, 1507-1879 or 83-1879 of a 1957 bp sequence (S1), reproduced, or its complements. (S1) encodes the zapop2 protein which includes a RING finger and **ankyrin repeat** motif. It has partial homology with the BRCA1 RING finger domain. (III) may also include a secretory signal sequence. Preferred Process: In (M1), a zapop2-expressing cell is transfected with a reporter gene construct that is responsive to a zapop2-**stimulated** cellular pathway, then treated with test sample, The responses, in presence or absence of sample, are compared in a biological or biochemical assay. In (M2), a sample is tested for hybridization to a fragment (Fr) containing at least 14 consecutive nucleotides of (1) and the result compared with that for a wild-type control. In (M3), cancer is indicated by (i) an altered level of binding of Ab or (ii) altered degree of hybridization of Fr to test samples, relative to controls. Preparation: A consensus RING finger motif was used to screen an EST (expressed sequence tag) database from **human** proteins. The initial EST was used to provide primers for

amplification of the full-length sequence (S1), from a peripheral blood granulocyte library. The zapop2 gene has been mapped to chromosome 1p36. Once isolated, the nucleic acid is expressed in usual vector-host systems.

ACTIVITY - Cardiant; hypotensive; angiogenic; cytostatic; vulnerary. No supporting data is given.

MECHANISM OF ACTION - None given.

USE - (I) is useful (i) for recombinant expression of (II), or for detecting genetic abnormalities in the genomic zapop2 sequence, particularly for diagnosis of cancer, and to prepare recombinant cells for detection/determination of zapop2 (ant)agonists (claimed). (I) can be used as probes and primers for cloning 5'-non-coding parts of the gene (potentially useful for directing heart and skeletal-muscle specific expression of heterologous sequences). (II) are used to raise specific antibodies (Ab); (I), (II), Ab and zapop2 agonists are used to treat a wide variety of **cardiac**/vascular disorders (e.g. myocardial infarction or congestive heart failure); to promote angiogenesis; to develop coronary co-lateral circulation and to revascularize the eye; to induce skeletal muscle neogenesis/hyperplasia, kidney regeneration and/or to treat systemic and pulmonary hypertension. Ab are also useful for diagnosis; purification of (II); screening expression libraries and producing antiidiotypic antibodies. Ab and (II) can also used to deliver drugs, toxins etc., for treatment or diagnosis of e.g. cancer.

ADMINISTRATION - Administration is parenteral or local. No dosage is given.

EXAMPLE - The initial EST sequence was contained in a plasmid and a partial sequence. An arrayed **human** salivary gland cDNA/plasmid library was screened by PCR (polymerase chain reaction) for zapop2 clones using primers ZC15M,399 and ZC15,400. Thermocycler conditions included one cycle at 94degreesC for 10 seconds, 60degreesC for 20 seconds, 72degreesC for 30 seconds and one cycle at 72degreesC for 7 mins. The library was deconvuluted down to a positive pool of 250 clones. E. coli cells were transformed with this pool by electroporation. The transformants were plated out to individual colonies and screened by PCR, where a positive clone comprising a full length zapop2 polynucleotide sequence of 1957 base pairs as given in the specification were identified and sequenced.(50 pages)

L13 ANSWER 21 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:449708 HCAPLUS
DOCUMENT NUMBER: 137:16513
TITLE: Promoters of **human** and mouse genes encoding **cardiac ankyrin repeat** proteins used for transgene expression in **cardiac** muscle cells for treatment of heart diseases
INVENTOR(S): Schwartz, Bertrand; Branellec, Didier; Chien, Kenneth
PATENT ASSIGNEE(S): Aventis Pharma S.A., Fr.; The Regents of the University of California; Benoit, Patrick; Chen, Ju
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002046220	A2	20020613	WO 2001-EP15412	20011205
WO 2002046220	A3	20030904		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB,
GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2431193	AA	20020613	CA 2001-2431193		20011205
AU 2002026400	A5	20020618	AU 2002-26400		20011205
BR 2001016014	A	20031021	BR 2001-16014		20011205
EP 1358208	A2	20031105	EP 2001-995724		20011205
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2004519222	T2	20040702	JP 2002-547956		20011205
FI 2003000851	A	20030606	FI 2003-851		20030606
NO 2003002584	A	20030805	NO 2003-2584		20030606
PRIORITY APPLN. INFO.:			US 2000-251582P	P	20001207
			WO 2001-EP15412	W	20011205

AB The invention relates to novel promoter sequences derived from a portion upstream of the coding sequence of the gene for the CARP protein (**Cardiac Ankyrin Repeat** Protein), and which are capable of controlling the level and the specificity of expression of a transgene in vivo in **cardiac** muscle cells. The invention thus describes novel compns., constructs, vectors and their uses in vivo for the transfer and expression of a nucleic acid in vivo in **cardiac** muscle cells. The subject of the present invention is also the use of the promoter sequences for generating transgenic animals which constitute models for studying certain **cardiac** pathologies.

L13 ANSWER 22 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:937303 HCAPLUS
DOCUMENT NUMBER: 138:20443
TITLE: Endocrine disruptor screening using DNA chips of endocrine disruptor-responsive genes
INVENTOR(S): Kondo, Akihiro; Takeda, Takeshi; Mizutani, Shigetoshi; Tsujimoto, Yoshimasa; Takashima, Ryokichi; Enoki, Yuki; Kato, Ikunoshin
PATENT ASSIGNEE(S): Takara Bio Inc., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 386 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
JP 2002355079	A2	20021210	JP 2002-69354		20020313
PRIORITY APPLN. INFO.:			JP 2001-73183	A	20010314
			JP 2001-74993	A	20010315
			JP 2001-102519	A	20010330

AB A method and kit for detecting endocrine-disrupting chems. using DNA microarrays are claimed. The method comprises preparing a nucleic acid sample containing mRNAs or cDNAs originating in cells, tissues, or organisms which have been brought into contact with a sample containing the endocrine disruptor. The nucleic acid sample is hybridized with DNA microarrays having genes affected by the endocrine disruptor or DNA fragments originating in these genes have been fixed. The results obtained are then compared with the results obtained with the control sample to select the gene affected by the endocrine disruptor. Genes whose expression is altered by tri-Bu tin, 4-octaphenol, 4-nonylphenol, di-N-Bu phthalate, dichlorohexyl phthalate, octachlorostyrene, benzophenone, diethylhexyl phthalate, diethylstilbestrol (DES), and 17-β estradiol (E2), were

found in mice by DNA chip anal.

L13 ANSWER 23 OF 40 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2002312728 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12054667
TITLE: **Cardiac ankyrin repeat** protein, a negative regulator of **cardiac** gene expression, is augmented in **human** heart failure.
AUTHOR: Zolk Oliver; Frohme Marcus; Maurer Alexander; Kluxen Franz-Werner; Hentsch Bernd; Zubakov Dimitri; Hoheisel Jorg D; Zucker Irving H; Pepe Salvatore; Eschenhagen Thomas
CORPORATE SOURCE: Institut fur Experimentelle und Klinische Pharmakologie und Toxikologie, Friedrich-Alexander-Universitat Erlangen-Nurnberg, Fahrstr. 17, 91054 Erlangen, Germany.. zolk@pharmakologie.uni-elargen.de
SOURCE: Biochemical and biophysical research communications, (2002 May 24) 293 (5) 1377-82.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020611
Last Updated on STN: 20020707
Entered Medline: 20020705

AB The technique of representational difference analysis of cDNA has been applied to screen for differentially expressed genes in a canine model of pacing-induced heart failure. We identified the canine homolog of the **cardiac ankyrin repeat** protein (CARP) which has been shown to be involved in the regulation of the transcription of **cardiac** genes. To confirm the significance for **human** heart failure, **cardiac** tissue specimens obtained from non-failing donor hearts and from explanted hearts from patients with end-stage heart failure were investigated. CARP mRNA and protein levels were markedly increased in failing left ventricles. Interestingly, alterations in CARP expression were restricted to ventricular tissue and were not observed in atria. Fractionation experiments revealed that CARP was expressed predominantly in the nuclei consistent with the proposed function of CARP as a **modulator** of transcription. Together, these findings raise the possibility that augmented ventricular CARP expression may play a role in the pathogenesis of **human** heart failure.

L13 ANSWER 24 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:151033 HCAPLUS
DOCUMENT NUMBER: 137:150897
TITLE: Biomarkers of **Human** Skin Cells Identified Using DermArray DNA Arrays and New Bioinformatics Methods
AUTHOR(S): Curto, Ernest V.; Lambert, Glenna W.; Davis, Richard L.; Wilborn, Teresa W.; Dooley, Thomas P.
CORPORATE SOURCE: IntegriDerm Inc., Huntsville, AL, 35801, USA
SOURCE: Biochemical and Biophysical Research Communications (2002), 291(4), 1052-1064
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Biomarker genes of **human** skin-derived cells were identified by new simple bioinformatic methods and DNA microarray anal. utilizing in vitro cultures of normal neonatal **human** epidermal keratinocytes, melanocytes, and dermal fibroblasts. A survey of 4405 **human**

cDNAs was performed using DermArray DNA microarrays. Biomarkers were rank ordered by "likelihood ratio" algorithms and stringent selection criteria that have general applicability for analyzing a min. of three RNA samples. Signature biomarker genes (up-regulated in one cell type) and anti-signature biomarker genes (down-regulated in one cell type) were determined for the three major skin cell types. Many of the signature genes are known biomarkers for these cell types. In addition, 17 signature genes were identified as ESTs, and 22 anti-signature biomarkers were discovered. Quant. RT-PCR was used to verify nine signature biomarker genes. A total of 158 biomarkers of normal **human** skin cells were identified, many of which may be valuable in diagnostic applications and as mol. targets for drug discovery and therapeutic intervention. (c) 2002 Academic Press.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 25 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:799085 HCAPLUS

DOCUMENT NUMBER: 138:50244

TITLE: Microarray analysis of VEGF-responsive genes in myometrial endothelial cells

AUTHOR(S): Weston, G. C.; Haviv, I.; Rogers, P. A. W.

CORPORATE SOURCE: Centre for Women's Health Research, Department of Obstetrics and Gynaecology, Monash University, Melbourne, Australia

SOURCE: Molecular Human Reproduction (2002), 8(9), 855-863 CODEN: MHREFD; ISSN: 1360-9947

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB There is evidence that the vasculature of different organs display different functional characteristics in response to cytokines and growth factors. The aim of this study was to use cDNA gene expression microarray to analyze changes in gene expression following **stimulation** of myometrial microvascular endothelial cells (MMECs) with vascular endothelial growth factor (VEGF). Primary isolates of MMECs were obtained from fresh hysterectomy specimens and purified with magnetic beads. Cells were **stimulated** with 15 ng/mL VEGF for 3, 6 and 12 h, and two unstimulated expts. served as controls. A total of six arrays was performed over these time-points. A total of 110 genes were identified as up-regulated by VEGF, 19% of which (21 genes) have previously been reported as up-regulated by VEGF or by angiogenesis. Among the novel genes to be up-regulated by VEGF were brain-derived growth factor, oxytocin receptor and estrogen sulfotransferase. The significance of the genes identified in the physiol. and pathol. functioning of the myometrial vasculature is discussed.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 26 OF 40 MEDLINE on STN DUPLICATE 9

ACCESSION NUMBER: 2002291255 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12031792

TITLE: Myotrophin-kappaB DNA interaction in the initiation process of **cardiac** hypertrophy.

AUTHOR: Gupta Sudhiranjan; Sen Subha

CORPORATE SOURCE: Department of Molecular Cardiology (NB 50), Lerner Research Institute, The Cleveland Clinic Foundation, 9500 Euclid Avenue, OH 44195, USA.

CONTRACT NUMBER: HL R01 47794 (NHLBI)

SOURCE: Biochimica et biophysica acta, (2002 May 8) 1589 (3) 247-60. Journal code: 0217513. ISSN: 0006-3002.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020529
Last Updated on STN: 20020829
Entered Medline: 20020827

AB To investigate how **cardiac** hypertrophy and heart failure develop, we isolated and characterized a candidate initiator, the soluble 12-kDa protein myotrophin, from rat and **human** hearts. Myotrophin **stimulates** protein synthesis and myocardial cell growth associated with increased levels of hypertrophy marker genes. Recombinant myotrophin from the cloned gene showed structural/functional motifs, including **ankyrin repeats** and putative phosphorylation sites for protein kinase C (PKC) and casein kinase II. One repeat, homologous with I kappaB, interacts with rel/NF-kappaB in vitro. We analyzed the interaction of recombinant myotrophin and nuclear extracts prepared from neonatal and adult cardiomyocytes; gel mobility shift assay showed that myotrophin bound to kappaB DNA. To define PKC's role in myotrophin-induced myocyte growth, we incubated neonatal rat myocytes (normal and stretch) with specific **inhibitors** and found that myotrophin **inhibits** [3H]leucine incorporation into myocytes and different hypertrophic gene expression in neonatal myocytes. Using confocal microscopy, we observed that a basal level of myotrophin was present in both cytoplasm and nucleus under normal conditions, but under cyclic stretch, myotrophin levels became elevated in the nucleus. Myotrophin gene levels were upregulated when myocytes underwent cyclic stretch or were treated with tumor necrosis factor-alpha (TNF-alpha) or interleukin-1beta and also when excised beating hearts were exposed to high pressure. Our data showed that the myotrophin-kappaB interaction was increased with age in spontaneously hypertensive rats (SHRs) only. Our data provide evidence that myotrophin-kappaB DNA interaction may be an important step in initiating **cardiac** hypertrophy.

L13 ANSWER 27 OF 40 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 2002626273 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12384280
TITLE: Alpha(1)-adrenergic **activation** of the **cardiac ankyrin repeat** protein gene in **cardiac** myocytes.
AUTHOR: Maeda Tomoji; Sepulveda Jorge; Chen Hsiao-Huei; Stewart Alexandre F R
CORPORATE SOURCE: Cardiovascular Institute, University of Pittsburgh, Pittsburgh, PA 15213, USA.
CONTRACT NUMBER: R29 HL57211 (NHLBI)
SOURCE: Gene, (2002 Sep 4) 297 (1-2) 1-9.
Journal code: 7706761. ISSN: 0378-1119.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF478692
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20021018
Last Updated on STN: 20030211
Entered Medline: 20030210

AB **Cardiac ankyrin repeat** protein (CARP) is a nuclear transcription cofactor that is **activated** by multiple signaling pathways in hypertrophic **cardiac** myocytes. Since CARP has been reported to be a transcriptional co-repressor, its **activation** during hypertrophy might contribute to the deregulation of gene expression leading to heart failure. Here, we found that alpha(1)-adrenergic signaling **activates** CARP mRNA expression in

rat **cardiac** myocytes. To examine how alpha(1)-adrenergic signaling **activates** the CARP gene, a 660 bp fragment of the mouse CARP promoter was cloned. Previous reports suggested that the mouse CARP promoter was dependent on the GATA4 transcription factor whereas the **human** CARP promoter was dependent on transcriptional enhancer factor-1 (TEF-1). TEF-1 and GATA4 transcription factors, known mediators of alpha(1)-adrenergic signaling, bound to the mouse CARP promoter at several sites as determined by gel mobility shift assays. These sites are highly conserved between the mouse and **human** promoters, suggesting that they are functionally important in both. Mutation analysis showed that binding of TEF-1 factors is required for basal activity of the CARP promoter in **cardiac** myocytes. However, over-expression of TEF-1 factors could not potentiate the response of the CARP promoter to alpha(1)-adrenergic **stimulation**. On the other hand, the alpha(1)-adrenergic response was potentiated by GATA4 over-expression. Taken together, our results demonstrate that alpha(1)-adrenergic signaling regulates CARP expression in **cardiac** myocytes, in part through the transcription factor GATA4.

L13 ANSWER 28 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:243586 HCAPLUS
DOCUMENT NUMBER: 137:305429
TITLE: Genomic organization of the **human** Arpp gene
AUTHOR(S): Miyazaki, Akiko; Tsukamoto, Yoshiyuki; Sato, Kenzo; Ohgi, Shigetsugu; Moriyama, Masatsugu
CORPORATE SOURCE: Department of Molecular Biology, Tottori University Faculty of Medicine, Yonago, 683-8503, Japan
SOURCE: Yonago Acta Medica (2002), 45(1), 1-8
CODEN: YOAMAQ; ISSN: 0513-5710
PUBLISHER: Tottori University Faculty of Medicine
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A novel ankyrin-repeated protein, Arpp, is specifically expressed in skeletal and **cardiac** muscles. Arpp protein is homologous, in its amino acid sequences (52.7% identity), to Carp protein which is proposed to be a putative genetic marker for **cardiac** hypertrophy. In this study, we isolated the **human** Arpp gene by screening a **human** genomic library and analyzed the genomic structure and its 5' flanking region. The Arpp gene was found to encompass a sequence of 11 kb and to consist of 9 exons. The translational initiation site and the stop codon were found to be located at exon 1 and exon 9, resp. Each exon from 5 to 8 was found to encode 1 of the 4 ankyrin-like domains, resp. The 2.7 kb upstream of exon 1 was sequenced. The TATA box was identified 29 bp upstream of the transcriptional start site, and multiple putative regulatory elements, including the E box and upstream **stimulating** factor-1 were distributed within the proximal promoter regions. Since these elements were also found in the promoter region of the mouse Arpp gene, they may play an important role in the transcriptional regulation of both **human** and murine Arpp genes.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 29 OF 40 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2002-06727 BIOTECHDS
TITLE: Novel 33358 polypeptide, a **human** ankyrin family member, useful as reagents or targets for treating and/or diagnosing myocardial infarction, restenosis, angina, aortic valve stenosis, raynaud's syndrome, psoriasis;
vector-mediated gene transfer, expression in host cell, DNA array and transgenic animal for recombinant protein production, drug screening, tissue typing and disease gene therapy

AUTHOR: GLUCKSMANN M A; KADAMBI V J
PATENT ASSIGNEE: MILLENNIUM PHARM INC
PATENT INFO: WO 2001096375 20 Dec 2001
APPLICATION INFO: WO 2000-US19591 16 Jun 2000
PRIORITY INFO: US 2000-212222 16 Jun 2000
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-139705 [18]

AB DERWENT ABSTRACT:

NOVELTY - An isolated 33358 polypeptide (a **human** ankyrin family member, referred to as **cardiac**/skeletal muscle-restricted **ankyrin-repeat** containing protein (C/SKARP)-1), (I,) comprising a fragment which comprises 10 contiguous amino acids of a fully defined sequence of 323 amino acids (S2), or comprising 60% identity to (S2), is new.

DETAILED DESCRIPTION - Where (I): (a) comprises a fragment which comprises 10 contiguous amino acids of a fully defined sequence of 323 amino acids (S2); (b) is a naturally occurring allelic variant of (S2) which is encoded by a nucleic acid molecule that hybridizes to a complement of a fully defined sequence of 1538 (S1) or 972 (S3) nucleotides under stringent conditions: (c) is a polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 60% identical to a nucleotide sequence of (S1) or (S3); or (d) is a polypeptide comprising an amino acid sequence which is 60% identical to (S2). INDEPENDENT CLAIMS are also included for the following: (1) an isolated nucleic acid molecule (II); (2) an isolated nucleic acid molecule which hybridizes to a complement of (II) under stringent conditions; (3) an isolated nucleic acid molecule comprising a nucleotide sequence which is complementary to (II); (4) an isolated nucleic acid molecule comprising (II) and a nucleotide sequence encoding a heterologous polypeptide; (5) a vector (III) comprising (II); (6) a host cell (IV) transfected with (III); (7) preparation of (I); (8) an antibody (V) which selectively binds to (I); (9) detecting (M1) presence of (II) in a sample; (10) a kit comprising a compound which selectively binds to (I) or a compound which selectively hybridizes to (II), and instructions for use; and (11) modulating the activity of (I) involves contacting the polypeptide or a cell expressing a polypeptide with a compound which binds to the polypeptide to modulate the activity of the polypeptide.

WIDER DISCLOSURE - The following are disclosed: (A) fusion proteins comprising 33358 polypeptide fused to non-33358 polypeptides; (B) an array comprising 33358 sequence, which is used to assay expression of one or more genes in the array; (C) nucleic acid molecules that differ from (II) due to degeneracy of genetic code; (D) nucleic acid variants which are homologs or orthologs of (S1) or (S3); (E) nucleic acid molecules encoding other 33358 family members which have a nucleotide sequence that differs from (S1) or (S3); (F) nucleic acid molecules encoding 33358 proteins that contain changes in amino acid residues that are not essential for activity; (G) variants of 33358 polypeptide which functions as agonist or antagonist; (H) non-**human** transgenic animals; (I) novel agents identified by screening methods involving (I); (J) a machine-readable medium e.g., a magnetic, optical, chemical or mechanical information storage device provided with 33358 sequences; (K) a medium for holding instructions for determining whether a subject has a 33358-associated disease or disorder or a predisposition to 33358-associated disease or disorder; (L) an electronic system and/or a network for determining whether a subject has a 33358-associated disease or disorder or a predisposition to 33358-associated disease or disorder; (M) a network for determining whether a subject has a 33358-associated disease or disorder or a predisposition to 33358-associated disease or disorder; (N) determining whether a subject has a 33358-associated disease or disorder or a predisposition to 33358-associated disease or disorder using the above mentioned network; and (O) assays for

determining the presence or absence of a genetic alteration in 33358 polypeptide or nucleic acid molecule.

BIOTECHNOLOGY - Preparation: (I) is prepared by standard recombinant techniques (claimed). Preferred Vector: (III) is an expression vector. Preferred Polypeptide: (I) preferably comprises an amino acid sequence of (S2) and further comprises heterologous amino acid sequences. (II), which: (a) comprises a sequence of (S1) or (S3); (b) encodes a polypeptide comprising an amino acid sequence of (S2); (c) encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of (S2); (d) comprises a nucleotide sequence which is 60% identical to (S1) or (S3) or its complement; (e) is a fragment comprising at least 30 nucleotides of (S1) or (S3) or its complement; (f) encodes a polypeptide comprising an amino acid sequence which is at least 60% identical to (S2); or (g) encodes a fragment of (S2) which comprises 10 contiguous amino acids of (S2); Preferred Method: In (M1), a sample comprising mRNA molecules is contacted with a nucleic acid probe. (9) comprises contacting the sample with a nucleic acid probe or primer which selectively hybridizes to the complement of the nucleic acid molecule in the sample to thereby detect the presence of (II) in the sample. Preferred Transgenic: (H) where an endogenous 33358 gene has been altered by homologous recombination between an endogenous gene and an exogenous DNA molecule introduced into a cell of the animal.

ACTIVITY - Antiarteriosclerotic; vasotropic; antianginal; cardiant; antiarrhythmic; hypotensive; cytostatic; antitumor; antipsoriatic; antidiabetic; ophthalmological; gynecological; antithyroid; antirheumatic; antiarthritic.

MECHANISM OF ACTION - Gene therapy; 33358 polypeptide expression or activity **modulator**.

USE - (I) is useful for identifying a compound which binds to it which involves contacting a polypeptide or a cell expressing a polypeptide with a test compound and determining whether the polypeptide binds to the test compound. The binding of test compound to the polypeptide is detected by directly detecting test compound/polypeptide binding, or by competition binding assay, or by using an assay for C/SKARP-1 activity. (I) is useful for identifying a compound which modulates its activity which involves contacting (I) with a test compound and determining the effect of the test compound on the activity of the polypeptide, to thereby identify a compound which modulates the activity of the polypeptide. (IV) is useful for producing (I) by recombinant techniques. (V) is useful for detecting the presence of (I) in a sample which involves contacting the sample with a compound (i.e., (V)) which selectively binds to (I) and determining whether (V) binds to the polypeptide in the sample (all claimed). The sequences of (I) and (II) are useful as query sequences to perform a search against public databases to identify other family members or related sequences. (I) is useful for treating disorders characterized by insufficient or excessive production of a 33358 substrate or for producing 33358 **inhibitors** , screening for drugs or compounds which modulate 33358 activity. (I) has the following activities: (i) mediation of specific macromolecular interactions; (ii) mediation of interactions between proteins and/or between regions of a single protein; (iii) formation of binding sites for distinct proteins (e.g., non-C/SKARP proteins); (iv) bridging of cellular components; (v) regulation of gene expression (e.g., **cardiac** gene expression) and, thus, can be used to, for example: (a) modulate cellular localization (e.g., anchoring C/SKARP binding proteins in a specific cellular localization); (b) modulate development and/or differentiation (e.g., myogenic development and/or differentiation, heart development and/or differentiation); (c) modulate **cardiac** maturation and/or morphogenesis; (d) as a marker (e.g., an early marker) of **cardiac** and/or myogenic cell lineage; and (e) modulate and/or treat C/SKARP-1-associated or related disorders. (II) is useful for expressing (I) via a recombinant expression vector in a host cell in gene therapy applications, to detect 33358 mRNA, or genetic alteration in

33358 gene and to modulate 33358 activity. Fragments of (II) are useful as probes and primers. Portions or fragments of (II) are useful to: (i) map their respective genes on a chromosome, e.g., to locate gene regions associated with genetic disease or to associate 33358 with a disease; (ii) identify an individual from a minute biological sample (tissue typing); (iii) aid in forensic identification of a biological sample. (II) can be inserted into vectors and used as gene therapy vectors. (V) is useful for isolating (I), to detect (I), to evaluate the abundance and pattern of expression of the protein, to diagnostically monitor protein levels in tissue, as a part of a clinical testing procedure, e.g., to determine the efficacy of a given treatment regimen. (V) is also useful for isolating 33358 proteins, regulating the bioavailability of 33358 proteins and modulating 33358 activity. (I), (II) and (V) are useful for: (a) screening assays; (b) predictive medicine (e.g., diagnostic assays, prognostic assays, monitoring clinical trials, and pharmacogenetics); and (c) methods of treatment (e.g., therapeutic and prophylactic). 33358 molecules ((I), (II), (V)) are useful as a novel diagnostic target and therapeutic agent in assays applicable to treatment and diagnosis of 33358 mediated or related disorders such as **cardiac** hypertrophy, **cardiac** disorders and/or cardiovascular disease, (e.g., congestive heart failure, cardiomyopathy), arteriosclerosis, ischemia reperfusion injury, restenosis, tachycardia, bradycardia, angina, hypertension, myocardial infarction, coronary artery disease, ischemic disease, raynaud's syndrome, aneurysm, aortic valve stenosis. A cardiovascular disease or disorder also includes an endothelial cell disorder, and thus the molecules are useful for treating the endothelial cell disorder such as tumorigenesis, tumor metastasis, psoriasis, diabetic retinopathy, endometriosis, Grave's disease, ischemic disease (e.g., atherosclerosis), and chronic inflammatory diseases (e.g., rheumatoid arthritis). The 33358 molecules are useful as surrogate markers for one or more disorders or disease states or for conditions leading up to disease states, as pharmacodyanamic markers and as pharmacogenomic markers.

ADMINISTRATION - Pharmaceutical compositions comprising (I), (II) and (V) are administered by parenteral, e.g., intravenous, intradermal, subcutaneous, oral, e.g., inhalation, transdermal, transmucosal or rectal route. No specific clinical dosages are given.

EXAMPLE - Gene encoding novel members of the acetyltransferase family, e.g., gene encoding **human cardiac**/skeletal muscle-restricted **ankyrin-repeat** containing protein (C/SKARP)-1 (also referred to as clone Fbh33358) was discovered. The nucleotide sequences encoding the **human** C/SKARP-1 protein. The C/SKARP-1 protein encoded by this nucleic acid comprised 323 amino acids (S2). The C/SKARP-1 coding region had a fully defined sequence of 972 nucleotides (S3) as given in the specification. A search was performed against the hidden Markov model (HMM) database resulting in the identification of six **ankyrin repeats** (i.e., an **ankyrin repeat** domain) in the amino acid sequence of **human** C/SKARP-1 at about residues 64-259 of (S2). Six ankyrin domains (Ank domain) were identified in the amino acid sequence of C/SKARP-1 at about residues 64-96; at about residues 97-129; at about residues 130-162; at about residues 165-194; at about residues 195-227 and at about residues 229-259. C/SKARP-1 also included potential casein kinase II phosphorylation sites, for example, from amino acid residues 101-104, 239-242, 263-266 and 272-275 of (S2). A potential tyrosine kinase phosphorylation site was found from about amino acid residues 50-56 of (S2). Potential N-myristoylation sites were found from amino acid residues 58-63, 88-93, 108-113, 121-126 and 142-147 of (S2). Dileucine motifs were found from amino acid residues 26-27, 34-35, 78-79, 117-118, 150-151, 182-183, 215-216, 246-247, 278-279 and 279-280 of (S2). Tissue distribution of C/SKARP-1 mRNA was determined by reverse transcriptase (RT)-PCR or by Northern blot analysis. From this analysis it was determined that C/SKARP-1 mRNA was expressed predominantly in

heart libraries, from both normal and congestive heart failure samples. C/SKARP-1 mRNA was found to a lesser extent in melanocytes and esophagus. (115 pages)

L13 ANSWER 30 OF 40 SCISEARCH

ACCESSION NUMBER: 2001:631570 SCISEARCH
THE GENUINE ARTICLE: 458VV
TITLE: Gene program for **cardiac** cell survival induced by transient ischemia in conscious pigs
AUTHOR: Depre C (Reprint); Tomlinson J E; Kudej R K; Gaussin V; Thompson E; Kim S J; Vatner D E; Topper J N; Vatner S F
CORPORATE SOURCE: Hackensack Univ, Med Ctr, Inst Cardiovasc Res, Res Bldg, Room 338, 30 Prospect Ave, Hackensack, NJ 07601 USA (Reprint); Hackensack Univ, Med Ctr, Inst Cardiovasc Res, Hackensack, NJ 07601 USA; Univ Med & Dent New Jersey, New Jersey Med Sch, Dept Med, Inst Cardiovasc Res, Newark, NJ 07103 USA; COR Therapeut Inc, S San Francisco, CA 94080 USA
COUNTRY OF AUTHOR: USA
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (31 JUL 2001) Vol. 98, No. 16, pp. 9336-9341.
Publisher: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418 USA.
ISSN: 0027-8424.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 47
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Therapy for ischemic heart disease has been directed traditionally at limiting cell necrosis. We determined by genome profiling whether ischemic myocardium can trigger a genetic program promoting **cardiac** cell survival which would be a novel and potentially equally important mechanism of salvage. Although **cardiac** genomics is usually performed in rodents, we used a swine model of ischemia/reperfusion followed by ventricular dysfunction (stunning), which more closely resembles clinical conditions. Gene expression profiles were compared by subtractive hybridization between ischemic and normal tissue of the same hearts. About one-third (23/74) of the nuclear-encoded genes that were upregulated in ischemic myocardium participate in survival mechanisms (**inhibition** of apoptosis, cytoprotection, cell growth, and **stimulation** of translation). The specificity of this response was confirmed by Northern blot and quantitative PCR. Unexpectedly, this program also included genes not previously described iri cardiomyocytes. Up-regulation of survival genes was more profound in subendocardium over subepicardium, reflecting that this response in stunned myocardium was proportional to the severity of the ischemic insult. Thus, in a swine model that recapitulates **human** heart disease, nonlethal ischemia **activates** a genomic program of cell survival that relates to the time course of myocardial stunning and differs transmurally in relation to ischemic stress, which induced the stunning. Understanding the genes up-regulated during myocardial stunning, including those not previously described in the heart, and developing strategies that **activate** this program may open new avenues for therapy in ischemic heart disease.

L13 ANSWER 31 OF 40 SCISEARCH

ACCESSION NUMBER: 2001:298964 SCISEARCH
THE GENUINE ARTICLE: 418UB
TITLE: Identification of a novel stretch-responsive skeletal muscle gene (Smpx)
AUTHOR: Kemp T J (Reprint); Sadusky T J; Simon M; Brown R;

Eastwood M; Sassoon D A; Coulton G R
CORPORATE SOURCE: Univ London Imperial Coll Sci Technol & Med, Natl Heart & Lung Inst, Dovehouse St, London SW3 6LY, England (Reprint); Univ London Imperial Coll Sci Technol & Med, Div Biomed Sci, London SW7 2AZ, England; Royal Free & Univ Coll Med Sch, Dept Surg, London NW3 2PF, England; CUNY Mt Sinai Sch Med, Dept Biochem & Mol Biol, New York, NY 10029 USA; Univ Coll London, Ctr Plast & Reconstruct Surg, Tissue Repair Unit, London WC1P 7LD, England; Univ Westminster, Dept Technol & Design, Ctr Tissue Engn Res, London W1M 8JS, England
COUNTRY OF AUTHOR: England; USA
SOURCE: GENOMICS, (15 MAR 2001) Vol. 72, No. 3, pp. 260-271.
Publisher: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA.
ISSN: 0888-7543.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 41
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Skeletal muscle is able to respond to a range of stimuli, including stretch and increased load, by increasing in diameter and length in the absence of myofiber division. This type of cellular growth (hypertrophy) is a highly complex process involving division of muscle precursor cells (myoblasts) and their fusion to existing muscle fibers as well as increased protein synthesis and decreased protein degradation. Underlying the alterations in protein levels are increases in a range of specific mRNAs including those coding for structural proteins and proteins that regulate the hypertrophic process. Seven days of passive stretch in vivo of tibialis anterior (TA) muscle has been shown to elicit muscle hypertrophy. We have identified a cDNA corresponding to an mRNA that exhibits increased expression in response to 7 days of passive stretch imposed on TA muscles in vivo, This 944-bp novel murine transcript is expressed primarily in **cardiac** and skeletal muscle and to a lesser extent in brain. Translation of the transcript revealed an open reading frame of 85 amino acids encoding a nuclear localization signal and two overlapping casein kinase II phosphorylation sites, This gene has been called "small muscle protein (X chromosome)" (Smpx; HGMW-approved **human** gene symbol SMPX) and we hypothesize that it plays a role in skeletal muscle hypertrophy, (C) 2001 Academic Press.

L13 ANSWER 32 OF 40 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 2001131490 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11139470
TITLE: Transforming growth factor-beta/Smads signaling induces transcription of the cell type-restricted **ankyrin repeat** protein CARP gene through CAGA motif in vascular smooth muscle cells.
COMMENT: Comment in: Circ Res. 2001 Jan 19;88(1):5-6. PubMed ID: 11139465
AUTHOR: Kanai H; Tanaka T; Aihara Y; Takeda S; Kawabata M; Miyazono K; Nagai R; Kurabayashi M
CORPORATE SOURCE: Second Department of Internal Medicine, Gunma University School of Medicine, Maebashi, Gunma, Japan.
SOURCE: Circulation research, (2001 Jan 19) 88 (1) 30-6.
Journal code: 0047103. ISSN: 1524-4571.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010521

Entered Medline: 20010301

AB Transforming growth factor (TGF)-beta plays a major role in the development of vascular diseases. Despite the pleiotropic effects of TGF-ss on vascular smooth muscle cells (VSMCs), only a few genes have been characterized as direct targets of TGF-beta in VSMCs. **Cardiac ankyrin repeat** protein (CARP) has been thought to be expressed exclusively in the heart. In the present study, we showed that CARP is expressed in the vasculature after balloon injury and in cultured VSMCs in response to TGF-beta. Analysis of a half-life of the cytoplasmic CARP mRNA levels and the transient transfection of the CARP promoter/luciferase gene indicates that the regulation of CARP expression is increased by TGF-beta at the transcriptional level. Transfection of expression vectors encoding Smads significantly **activated** the CARP promoter/luciferase activity. Deletion analysis and site-specific mutagenesis of the CARP promoter indicate that TGF-beta response element is localized to CAGA motif at -108 bp relative to the transcription start site. Electrophoretic mobility shift assays showed that the binding activity to the CAGA motif was increased in nuclear extracts of cultured VSMCs by TGF-beta. Cells transfected with adenovirus vector expressing CARP showed a significant decrease in DNA synthesis. Overexpression of CARP enhanced the TGF-beta-mediated **inhibition** of the DNA synthesis. These data indicate that CARP is a downstream target of TGF-beta/Smad signaling in VSMCs and suggest a role of CARP in mediation of the **inhibitory** effects of TGF-beta on the proliferation of VSMCs.

L13 ANSWER 33 OF 40 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:191240 HCAPLUS
DOCUMENT NUMBER: 132:247147
TITLE: Adenovirus vector for heart-specific gene expression and its use in gene therapy
INVENTOR(S): Chien, Kenneth R.; Wang, Yibin; Evans, Sylvia
PATENT ASSIGNEE(S): Regents of the University of California, USA
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2000015821	A1	20000323	WO 1999-US20730		19990910
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2342283	AA	20000323	CA 1999-2342283		19990910
CA 2342283	C	20040525			
AU 9958195	A1	20000403	AU 1999-58195		19990910
EP 1109925	A1	20010627	EP 1999-945628		19990910
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 2002525064	T2	20020813	JP 2000-570348		19990910
US 6451594	B1	20020917	US 1999-394110		19990910
PRIORITY APPLN. INFO.:			US 1998-99960P	P	19980911
			WO 1999-US20730	W	19990910

AB A **human** type-5 recombinant adenovirus vector Ad/CG/ITR for

heart-specific gene expression is constructed by using the promoter from the cardiomyocyte-restricted **cardiac ankyrin repeat** protein (CARP)in combination of the inverted terminal repeat (ITR) sequences from **human** adeno-associated virus (AAV). Using green fluorescent protein (GFP) as a marker gene, Ad/CG/ITR is shown to direct transgene expression to myocardial tissue in cultured cell lines, in the injected heart muscle and in developing mouse embryos (by microinjection into **cardiac** cavities). The inclusion of AAV ITR is required for tissue-specific expression and the gene expression is regulated at the transcription level. The promoters of other **cardiac** restricted genes are also suggested. These **cardiac**-specific adenovirus vector can be used in gene therapy of heart diseases.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ACCESSION NUMBER: 2000:605819 SCISEARCH
THE GENUINE ARTICLE: 340XK

TITLE: Doxorubicin represses CARP gene transcription through the generation of oxidative stress in neonatal rat **cardiac** myocytes: Possible role of serine/threonine kinase-dependent pathways

AUTHOR: Aihara Y; Kurabayashi M (Reprint); Tanaka T; Takeda S; Tomaru K; Sekiguchi K; Ohyama Y; Nagai R
CORPORATE SOURCE: GUNMA UNIV, SCH MED, DEPT INTERNAL MED 2, 3-39-15 SHOWA MACHI, GUNMA 3718511, JAPAN (Reprint); GUNMA UNIV, SCH MED, DEPT INTERNAL MED 2, GUNMA 3718511, JAPAN; UNIV TOKYO, GRAD SCH MED, DEPT CARDIOVASC MED, TOKYO, JAPAN
COUNTRY OF AUTHOR: JAPAN

SOURCE: JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY, (AUG 2000) Vol. 32, No. 8, pp. 1401-1414.
Publisher: ACADEMIC PRESS LTD, 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND.
ISSN: 0022-2828.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 51

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Doxorubicin (Dox), an anthracyclin antineoplastic agent, causes dilated cardiomyopathy. CARP has been identified as a nuclear protein whose mRNA levels are exquisitely sensitive to Dox. In this study we investigated the molecular mechanisms underlying the repression of CARP expression by Dox in cultured neonatal rat **cardiac** myocytes. Dox (1 mu mol/l)-mediated decrease in CARP mRNA levels was strongly correlated with BNP but not with ANP mRNA levels. Hydrogen peroxide scavenger catalase (1 mg/ml) but not hydroxyl radical scavengers dimethylthiourea (10 mmol/l) or mannitol (10 mmol/l) blunted the Dox-mediated decrease in CARP and BNP expression. Superoxide dismutase **inhibitor** diethyldithiocarbamic acid (10 mmol/l), which **inhibits** the generation of hydrogen peroxide from superoxide metabolism, attenuated the repression. PD98059 (MEK1 **inhibitor**, 50 mu mol/l), SB203580 (p38 MAP kinase **inhibitor**, 10 mu mol/l), calphostin C (protein kinase C (PKC) **inhibitor**, 1 mu mol/l), non-selective protein tyrosine kinase **inhibitors** genistein (50 mu mol/l) or herbimycin A (1 mu mol/l) failed to abrogate the downregulation of CARP and BNP expression by Dox. In contrast. H7 (30 mu mol/l), a potent **inhibitor** of serine/threonine kinase, significantly blocked Dox-mediated downregulation of CARP and BNP expression. Transient transfection of a series of 5'-deletion and site-specific mutation constructs revealed that M-CAT element located at -37 of the **human** CARP promoter mediates

Dox-induced repression of CARP promoter activity. These results suggest that a genetic response to Dox is mediated through the generation of hydrogen peroxide, which is selectively linked to the **activation** of H7-sensitive serine/threonine kinase distinct from PKC and well characterized mitogen-**activated** protein (MAP) kinases (ERK and p38MAP kinase). Furthermore, our data implicated M-CAT element as a Dox-response element within the CARP promoter in **cardiac** myocytes. (C) 2000 Academic Press.

L13 ANSWER 35 OF 40 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2000:385118 BIOSIS
DOCUMENT NUMBER: PREV200000385118
TITLE: **Cardiac ankyrin repeat** protein is a novel marker of **cardiac** hypertrophy: Role of M-CAT element within the promoter.
AUTHOR(S): Aihara, Yasushi; Kurabayashi, Masahiko [Reprint author]; Saito, Yuichiro; Ohyama, Yoshio; Tanaka, Toru; Takeda, Shin-ichi; Tomaru, Kouichi; Sekiguchi, Ken-ichi; Arai, Masashi; Nakamura, Tetsuya; Nagai, Ryozo
CORPORATE SOURCE: Second Department of Internal Medicine, Gunma University School of Medicine, 3-39-15, Showa-machi, Maebashi, Gunma, 371-8511, Japan
SOURCE: Hypertension (Baltimore), (July, 2000) Vol. 36, No. 1, pp. 48-53. print.
CODEN: HPRTDN. ISSN: 0194-911X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Sep 2000
Last Updated on STN: 8 Jan 2002

AB CARP, a **cardiac** doxorubicin (adriamycin)-responsive protein, has been identified as a nuclear protein whose expression is downregulated in response to doxorubicin. In the present study, we tested the hypothesis that CARP serves as a reliable genetic marker of **cardiac** hypertrophy in vivo and in vitro. CARP expression was markedly increased in 3 distinct models of **cardiac** hypertrophy in rats: constriction of abdominal aorta, spontaneously hypertensive rats, and Dahl salt-sensitive rats. In addition, we found that CARP mRNA levels correlate very strongly with the brain natriuretic peptide mRNA levels in Dahl rats. Transient transfection assays into primary cultures of neonatal rat **cardiac** myocytes indicate that transcription from the CARP and brain natriuretic peptide promoters is **stimulated** by overexpression of p38 and Rac1, components of the stress-**activated** mitogen-**activated** protein kinase pathways. Mutation analysis and electrophoretic mobility shift assays indicated that the M-CAT element can serve as a binding site for nuclear factors, and this element is important for the induction of CARP promoter activity by p38 and Rac1. Thus, our data suggest that M-CAT element is responsible for the regulation of the CARP gene in response to the **activation** of stress-responsive mitogen-**activated** protein kinase pathways. Moreover, given that **activation** of these pathways is associated with **cardiac** hypertrophy, we propose that CARP represents a novel genetic marker of **cardiac** hypertrophy.

L13 ANSWER 36 OF 40 MEDLINE on STN DUPLICATE 12

ACCESSION NUMBER: 97426428 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9278441
TITLE: A novel **cardiac**-restricted target for doxorubicin. CARP, a nuclear **modulator** of gene expression in **cardiac** progenitor cells and cardiomyocytes.
AUTHOR: Jeyaseelan R; Poizat C; Baker R K; Abdishoo S; Isterabadi L B; Lyons G E; Kedes L

CORPORATE SOURCE: Institute for Genetic Medicine and the Department of Biochemistry and Molecular Biology, University of Southern California School of Medicine, Los Angeles, California 90033, USA.
SOURCE: Journal of biological chemistry, (1997 Sep 5) 272 (36) 22800-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971013
Last Updated on STN: 19971013
Entered Medline: 19971002

AB Doxorubicin (Dox), a cardiotoxic antineoplastic drug, disrupts the **cardiac**-specific program of gene expression (Kurabayashi, M., Dutta, S., Jeyaseelan, R., and Kedes, L. (1995) Mol. Cell. Biol. 15, 6386-6397; Jeyaseelan, R., Poizat, C., Wu, H. Y., and Kedes, L. (1997) J. Biol. Chemical 272, 5828-5832). To determine whether this drug might interfere with the function of **cardiac**-specific regulatory pathways, we used a differential display strategy to clone from neonatal rat cardiomyocyte candidate mRNAs that were rapidly sensitive to Dox. We report here the identification of a constitutively expressed, **cardiac**-restricted, nuclear protein whose mRNA level is exquisitely sensitive to Dox. Hence we have named this protein **cardiac** adriamycin-responsive protein (CARP). CARP mRNA is present at the earliest stages of **cardiac** morphogenesis. It was detected by in situ hybridization within the cardiogenic plate of 7. 5-day post coitum (p.c.) embryos, and in 8.5-day p.c. embryos CARP transcripts are present in uniformly high levels in the myocardium. Throughout **cardiac** development, CARP expression is specific for the myocardium; endocardial cushions and valves exhibit only background levels of signal. Transcript levels persist but gradually decrease in neonatal, 2-week-old, and adult hearts. There were no stages when CARP mRNA could not be detected. The pattern and timing of CARP mRNA expression, including transient expression in the tongue at 14.5 days p.c., coincides with that of Nkx2.5/Csx (a putative homolog of tinman, the Drosophila melanogaster gene responsible for **cardiac** development). The cloned full-length 1749 nucleotide CARP cDNA encodes a 319-amino acid 40-kDa polypeptide containing five tandem **ankyrin** **repeats**. CARP appears to be the rat homolog of a previously reported **human** single-copy gene (C-193; Chu, W., Burns, D. K., Swerlick, R. A., and Presky, D. H. (1995) J. Biol. Chemical 270, 10236-10245), whose mRNA is inducible by cytokines only in **human** endothelial cells. CARP appears to function as a negative regulator of **cardiac**-specific gene expression. Overexpression of CARP in cardiomyocytes suppresses **cardiac** troponin C and atrial natriuretic factor transcription. Cotransfection experiments in HeLa cells indicate that CARP **inhibits** Nkx2.5 transactivation of atrial natriuretic factor promoter. When fused to a GAL4 DNA-binding domain, CARP has transcriptional **inhibitory** properties in noncardiac cells. CARP thus represents the first example of a **cardiac**-restricted transcriptional regulatory protein that is sensitive to Dox.

L13 ANSWER 37 OF 40 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 97337457 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9194197
TITLE: Nuclear magnetic resonance assignment and secondary structure of an **ankyrin**-like **repeat** -bearing protein: myotrophin.
AUTHOR: Yang Y; Rao N S; Walker E; Sen S; Qin J

CORPORATE SOURCE: Department of Molecular Cardiology, Cleveland Clinic Foundation, Ohio 44195, USA.
SOURCE: Protein science : a publication of the Protein Society, (1997 Jun) 6 (6) 1347-51.
Journal code: 9211750. ISSN: 0961-8368.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970825
Last Updated on STN: 20000303
Entered Medline: 19970813

AB Multidimensional heteronuclear NMR has been applied to the structural analysis of myotrophin, a novel protein identified from spontaneously hypertensive rat hearts and hypertrophic **human** hearts. Myotrophin has been shown to **stimulate** protein synthesis in myocytes and likely plays an important role in the initiation of **cardiac** hypertrophy, a major cause of mortality in **humans** . Recent cDNA cloning revealed that myotrophin has 11B amino acids containing 2.5 contiguous ANK repeats, a motif known to be involved in a wide range of macromolecular recognition. A series of two- and three-dimensional heteronuclear bond correlation NMR experiments have been performed on uniformly 15N-labeled or uniformly 15N/13C-labeled protein to obtain the 1H, 15N, and 13C chemical shift assignments. The secondary structure of myotrophin has been determined by a combination of NOEs, NH exchange data, 3JHN alpha coupling constants, and chemical shifts of 1H alpha, 13C alpha, and 13 C beta. The protein has been found to consist of seven helices, all connected by turns or loops. Six of the seven helices (all but the C-terminal helix) form three separate helix-turn-helix motifs. The two full ANK repeats in myotrophin are characteristic of multiple turns followed by a helix-turn-helix motif. A hairpin-like turn involving L32-R36 in ANK repeat #1 exhibits slow conformational averaging on the NMR time scale and appears dynamically different from the corresponding region (D65-169) of ANK repeat #2.

L13 ANSWER 38 OF 40 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 1998044226 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9382869
TITLE: Accumulation of muscle **ankyrin repeat** protein transcript reveals local **activation** of primary myotube endcompartments during muscle morphogenesis.
AUTHOR: Baumeister A; Arber S; Caroni P
CORPORATE SOURCE: Friedrich Miescher Institute, P.O. Box 2543, CH-4002 Basel, Switzerland.
SOURCE: Journal of cell biology, (1997 Dec 1) 139 (5) 1231-42.
Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980116
Last Updated on STN: 19980116
Entered Medline: 19971230

AB The characteristic shapes and positions of each individual body muscle are established during the process of muscle morphogenesis in response to patterning information from the surrounding mesenchyme. Throughout muscle morphogenesis, primary myotubes are arranged in small parallel bundles, each myotube spanning the forming muscles from end to end. This unique arrangement potentially assigns a crucial role to primary myotube end regions for muscle morphogenesis. We have cloned muscle **ankyrin**

repeat protein (MARP) as a gene induced in adult rat skeletal muscle by denervation. MARP is the rodent homologue of **human** C-193 (Chu, W., D.K. Burns, R.A. Swerick, and D.H. Presky. 1995. J. Biol. Chemical 270:10236-10245) and is identical to rat **cardiac ankyrin repeat** protein. (Zou, Y., S. Evans, J. Chen, H.-C. Kuo, R.P. Harvey, and K.R. Chien. 1997. Development. 124:793-804). In denervated muscle fibers, MARP transcript accumulated in a unique perisynaptic pattern. MARP was also expressed in large blood vessels and in **cardiac** muscle, where it was further induced by **cardiac** hypertrophy. During embryonic development, MARP was expressed in forming skeletal muscle. In situ hybridization analysis in mouse embryos revealed that MARP transcript exclusively accumulates at the end regions of primary myotubes during muscle morphogenesis. This closely coincided with the expression of thrombospondin-4 in adjacent prospective tendon mesenchyme, suggesting that these two compartments may constitute a functional unit involved in muscle morphogenesis. Transfection experiments established that MARP protein accumulates in the nucleus and that the levels of both MARP mRNA and protein are controlled by rapid degradation mechanisms characteristic of regulatory early response genes. The results establish the existence of novel regulatory muscle fiber subcompartments associated with muscle morphogenesis and denervation and suggest that MARP may be a crucial nuclear cofactor in local signaling pathways from prospective tendon mesenchyme to forming muscle and from **activated** muscle interstitial cells to denervated muscle fibers.

L13 ANSWER 39 OF 40 MEDLINE on STN

ACCESSION NUMBER:	97195688 MEDLINE
DOCUMENT NUMBER:	PubMed ID: 9043061
TITLE:	CARP, a **cardiac ankyrin repeat** protein, is downstream in the Nkx2-5 homeobox gene pathway.
AUTHOR:	Zou Y; Evans S; Chen J; Kuo H C; Harvey R P; Chien K R
CORPORATE SOURCE:	American Heart Association-Bugher Foundation Center for Molecular Biology, Department of Medicine, University of California, San Diego, La Jolla 92093, USA.
SOURCE:	Development (Cambridge, England), (1997 Feb) 124 (4) 793-804. Journal code: 8701744. ISSN: 0950-1991.
PUB. COUNTRY:	ENGLAND: United Kingdom
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
OTHER SOURCE:	GENBANK-AF041847
ENTRY MONTH:	199703
ENTRY DATE:	Entered STN: 19970414 Last Updated on STN: 20000303 Entered Medline: 19970331

AB To identify the molecular pathways that guide **cardiac** ventricular chamber specification, maturation and morphogenesis, we have sought to characterize factors that regulate the expression of the ventricular myosin light chain-2 gene, one of the earliest markers of ventricular regionalization during mammalian cardiogenesis. Previously, our laboratory identified a 28 bp HF-la/MEF-2 element in the MLC-2v promoter region, which confers **cardiac** ventricular chamber-specific gene expression during murine cardiogenesis, and showed that the ubiquitous transcription factor YB-1 binds to the HF-la site in conjunction with a co-factor. In a search for interacting co-factors, a nuclear **ankyrin**-like **repeat** protein CARP (**cardiac ankyrin repeat** protein) was isolated from a rat neonatal heart cDNA library by yeast two-hybrid screening, using YB-1 as the bait. Co-immunoprecipitation and GST-CARP pulldown studies reveal that CARP forms a physical complex with YB-1 in **cardiac** myocytes and immunostaining shows that endogenous CARP is localized in the **cardiac** myocyte nucleus. Co-transfection

assays indicate that CARP can negatively regulate an HF-1-TK minimal promoter in an HF-1 sequence-dependent manner in **cardiac** myocytes, and CARP displays a transcriptional **inhibitory** activity when fused to a GAL4 DNA-binding domain in both **cardiac** and noncardiac cell context. Northern analysis revealed that carp mRNA is highly enriched in the adult heart, with only trace levels in skeletal muscle. During murine embryogenesis, endogenous carp expression was first clearly detected as early as E8.5 specifically in heart and is regulated temporally and spatially in the myocardium. Nkx2-5, the murine homologue of Drosophila gene tinman was previously shown to be required for heart tube looping morphogenesis and ventricular chamber-specific myosin light chain-2 expression during mammalian heart development. In Nkx2-5(-/-)embryos, carp expression was found to be significantly and selectively reduced as assessed by both whole-mount in situ hybridizations and RNase protection assays, suggesting that carp is downstream of the homeobox gene Nkx2-5 in the **cardiac** regulatory network. Co-transfection assays using a dominant negative mutant Nkx2-5 construct with CARP promoter-luciferase reporter constructs in **cardiac** myocytes confirms that Nkx2-5 either directly or indirectly regulates carp at the transcriptional level. Finally, a carp promoter-lacZ transgene, which displays **cardiac**-specific expression in wild-type and Nkx2-5(+/-) background, was also significantly reduced in Nkx2-5(-/-) embryos, indicating that Nkx2-5 either directly or indirectly regulates carp promoter activity during in vivo cardiogenesis as well as in cultured **cardiac** myocytes. Thus, CARP is a YB-1 associated factor and represents the first identified **cardiac**-restricted downstream regulatory gene in the homeobox gene Nkx2-5 pathway and may serve as a negative regulator of HF-1-dependent pathways for ventricular muscle gene expression.

L13 ANSWER 40 OF 40 MEDLINE on STN DUPLICATE 15

ACCESSION NUMBER:	96162029 MEDLINE
DOCUMENT NUMBER:	PubMed ID: 8576259
TITLE:	**Cardiac** myotrophin exhibits rel/NF-kappa B interacting activity in vitro.
AUTHOR:	Sivasubramanian N; Adhikary G; Sil P C; Sen S
CORPORATE SOURCE:	Department of Molecular Cardiology, Cleveland Clinic Foundation, Ohio 44195, USA.. sivasun@cesmtp.ccf.org
CONTRACT NUMBER:	HL 47794 (NHLBI)
SOURCE:	Journal of biological chemistry, (1996 Feb 2) 271 (5) 2812-6. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
OTHER SOURCE:	GENBANK-U21661
ENTRY MONTH:	199603
ENTRY DATE:	Entered STN: 19960321 Last Updated on STN: 20000303 Entered Medline: 19960312

AB Myotrophin is a soluble-12 kilodalton protein isolated from hypertrophied spontaneously hypertensive rat and dilated cardiomyopathic **human** hearts. We have recently cloned the gene coding for myotrophin and expressed it in Escherichia coli. In the present study, the expression of myotrophin gene was analyzed, and at least seven transcripts have been detected in rat heart and in other tissues. We have further analyzed the primary structure of myotrophin protein and identified significant new structural and functional domains. Our analysis revealed that one of the **ankyrin repeats** of myotrophin is highly homologous specifically to those of myotrophin is highly homologous specifically to those of I kappa B alpha/rel **ankyrin repeats**. In addition, putative consensus phosphorylation sites for protein kinase C

and casein kinase II, which were observed in I kappa B alpha proteins, were identified in myotrophin. To verify the significance of these homologies, kappa B gel shift assays were performed with Jurkat T cell nuclear extract proteins and the recombinant myotrophin. Results of these assays indicate that the recombinant myotrophin has the ability to interact with NF-kappa B/rel proteins as revealed by the formation of ternary protein-DNA complexes. While myotrophin-specific antibodies **inhibited** the formation of these complexes, rel-specific p50 and p65 antibodies supershifted these complexes. Thus, these results clearly indicate that the myotrophin protein to be a unique rel/NF-kappa B interacting protein.

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=> d his

     (FILE 'HOME' ENTERED AT 13:55:08 ON 13 APR 2005)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 13:55:36 ON 13 APR 2005
L1           17 S "CARK"
L2         1949 S "CARDIAC-RELATED"
L3         4025 S ANKYRIN(2W)REPEAT
L4            4 S L2 AND L3
L5            3 DUP REM L4 (1 DUPLICATE REMOVED)
L6           15 DUP REM L1 (2 DUPLICATES REMOVED)
L7     11583440 S MODULATOR? OR INHIBIT? OR ACTIVAT? OR STIMULAT?
L8         4037 S CARDIAC (2W) RELATED
L9            4 S L8 AND ANKYRIN
L10        2200 S L3 AND L7
L11        1035 S HUMAN AND L10
L12          87 S CARDIAC AND L11
L13          40 DUP REM L12 (47 DUPLICATES REMOVED)

=> e raju j/au
E1           18      RAJU I V K BHAGAVAN/AU
E2            3      RAJU IVATURY S/AU
E3          111 --> RAJU J/AU
E4            1      RAJU J A S/AU
E5            1      RAJU J AYYAPA/AU
E6            5      RAJU J AYYAPPA/AU
E7            1      RAJU J B/AU
E8            3      RAJU J D/AU
E9            8      RAJU J M/AU
E10           3      RAJU J N/AU
E11          81      RAJU J R/AU
E12          11      RAJU J S/AU

=> s e3
L14         111 "RAJU J"/AU

=> s l13 and l14
L15           0 L13 AND L14

=> s (l2 or l3 or l1) and l14
L16           2 (L2 OR L3 OR L1) AND L14

=> d 1-2 ibib ab

L16   ANSWER 1 OF 2  BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2003-13047  BIOTECHDS
TITLE:               Novel isolated cardiac-related
                     ankyrin-repeat protein kinase polypeptide,
                     useful for treating cellular growth related disorders which
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include cardiovascular disorders and proliferative and/or differentiative disorders;
vector-mediated gene transfer and expression in host cell for recombinant protein production for use in disease diagnosis, gene therapy and pharmacogenomics

AUTHOR: **RAJU J**
PATENT ASSIGNEE: MILLENNIUM PHARM INC
PATENT INFO: WO 2003020912 13 Mar 2003
APPLICATION INFO: WO 2002-US28300 4 Sep 2002
PRIORITY INFO: US 2001-947199 5 Sep 2001; US 2001-947199 5 Sep 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2003-290188 [28]

AB DERWENT ABSTRACT:
NOVELTY - An isolated **cardiac-related ankyrin -repeat** protein kinase (**CARK**) polypeptide (I), comprising an allelic variant of a polypeptide having a sequence (S1) of 835 amino acids (aa), encoded by a nucleic acid molecule (NA) that hybridizes to a sequence (S2) of 3025, 2505 or 3026 base pairs, or a polypeptide encoded by a NA 60% homologous to S2, or fragment of S1, where S1 and S2 are given in specification, is new.

DETAILED DESCRIPTION - (I) is selected from a naturally occurring allelic variant of S1 encoded by a NA which hybridizes to NA comprising S2 under stringent conditions, a polypeptide encoded by a NA comprising a sequence which is at least 60% homologous to S2, a fragment comprising at least 15 contiguous (aa)s of S1, and a polypeptide comprising an (aa) sequence which is at least 60% homologous to S1. INDEPENDENT CLAIMS are also included for the following: (1) isolated NA (II) selected from a NA comprising a sequence of S2, a NA which encodes a polypeptide comprising S1, a NA comprising the sequence contained in the plasmid deposited with ATCC as Accession Number PTA-1530, a NA which encodes the naturally occurring allelic variant of S1, a NA comprising a sequence which is at least 60% homologous to S2 or its complement, a NA comprising a fragment of at least 467 nucleotides of S2 or its complement, a NA which encodes a polypeptide comprising a sequence at least about 60% homologous to S1, and a NA which encodes a fragment of S1, where the fragment comprises at least 15 contiguous (aa)s of S1; (2) an isolated NA which hybridizes to (II) under stringent conditions; (3) isolated NA comprising a sequence which is complementary to the sequence of (II); (4) isolated NA comprising (II), and a nucleotide sequence encoding a heterologous polypeptide; (5) vector (III) comprising (II); (6) host cell (HC) transfected with (III); (7) antibody (IV) which selectively binds (I); (8) production of (I); (9) detecting (M1) the presence of (II) in a sample by contacting the sample with a nucleic acid probe or primer which selectively hybridizes to (II), and determining whether the probe or primer binds to (II) in the sample; (10) kit (V) comprising a compound which selectively binds to (I) or hybridizes to (II), and instructions for use; and (11) modulating (M2) the activity of (I) by contacting (I) or a cell expressing (I) with a compound which binds to (I).

WIDER DISCLOSURE - Also disclosed are: (1) isolated NA antisense to (II); (2) diagnostic assay for identifying the presence or absence of a genetic alteration characterized by at least one of aberrant modification or mutation of a gene encoding a **CARK** protein, mis-regulation of the gene, and aberrant post-translational modification of a **CARK** protein; (3) nucleic acid molecule that differs from S2, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number PTA-1530; (4) a non-human ortholog of (I); (5) nucleic acid molecule encoding (I) that contains changes in (aa) residues that are not essential for activity; (6) **CARK** chimeric or fusion proteins; and (7) agent which modulates expression or activity of (I).

BIOTECHNOLOGY - Preparation: (I) is produced by culturing HC in an appropriate culture medium to produce (I) (claimed). Preferred

Polypeptide: (I) further comprises heterologous (aa) sequences. Preferred Vector: (III) is an expression vector. Preferred Method: In M1, the sample comprises mRNA molecules and is contacted with a nucleic acid probe.

ACTIVITY - Cardiant; Hypotensive; Cytostatic. No biological data is given.

MECHANISM OF ACTION - Gene therapy.

USE - (IV) is useful for detecting the presence of (I) in a sample by contacting the sample with (IV), and determining whether (IV) binds to (I) in the sample. (I) is useful for identifying a compound which binds to (I) by contacting (I), or a cell expressing (I) with a test compound, and determining whether (I) binds to the test compound. (I) is useful for identifying a compound which modulates the activity of (I) by contacting (I) with a test compound and determining the effect of the test compound on the activity of (I) (claimed). (I) or (II) is useful as modulating agents for regulating a variety of cellular processes, e.g., cardiac cellular process, for modulating the phosphorylation state of a **CARK** molecule or one or more proteins involved in cellular growth or differentiation, for modulating cell behavior or as targets and therapeutic agents controlling cardiac cell proliferation, differentiation, hypertrophy and migration, for modulating intra-or inter-cellular signaling and/or gene transcription, for modulating cell proliferation, growth, differentiation, survival and/or migration, for regulating transmission of signals from cellular receptors, for modulating entry of cells, e.g., cardiac precursor cells, into mitosis, or for regulating cytoskeletal function. (I) or (II) is useful for treating cellular growth related disorders which include cardiovascular disorders (such as heart failure, hypertension), and proliferative and/or differentiative disorders (such as cancer). (I), (II) or (IV) is useful in screening assays, detection assays (e.g., chromosomal mapping, tissue typing, forensic biology), predictive medicine (e.g., diagnostic assays, prognostic assays, monitoring clinical trials and pharmacogenomics), and in methods of treatment (e.g., therapeutic and prophylactic). (I) is useful as an immunogen to generate antibodies that bind (I). (I) is useful to screen for naturally occurring **CARK** substrates, and to screen for drugs or compounds which modulate **CARK** activity. (I) is useful as a bait protein in a yeast two-hybrid or three-hybrid assay and to identify other proteins which bind to or interact with **CARK** and or involved in the **CARK** activity. (II) is useful as hybridization probe to identify (II), or as polymerase chain reaction (PCR) primer for the amplification or mutation of (II). (II) is useful in gene therapy, to express (I), to detect **CARK** mRNA or a genetic alteration in a **CARK** gene, and to modulate **CARK** activity. (II) is useful to map their respective genes on a chromosome, e.g. to locate gene regions associated with genetic disease or to associate **CARK** with the disease, to identify an individual from a minute biological sample (tissue typing), and to aid in forensic identification of the biological sample. (I) or (II) is useful as a query sequence to perform a search against public databases to, for example, identify other family members or related sequences. HC is useful for producing non-human transgenic animals. (IV) is useful to isolate and purify (I), to detect (I) and to diagnostically monitor protein levels in tissue as part of a clinical testing procedure.

ADMINISTRATION - A pharmaceutical composition comprising (I), (II) or (V) is administered by parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), transmucosal, or rectal route at a dose of 0.001-30 mg/kg, preferably 1-10 mg/kg, more preferably 5-6 mg/kg.

EXAMPLE - Identification and characterization of the genes encoding human **cardiac-related ankyrin-repeat** protein kinase (**CARK**) and rat **CARK** was as follows: The human **CARK** gene was isolated from cDNA library which was prepared from tissue obtained from subjects suffering from

congestive heart failure of ischemic and idiopathic origin. Briefly, a cardiac tissue sample was obtained from a biopsy of four patients suffering from congestive heart failure. mRNA was isolated from the cardiac tissue and a cDNA library was prepared. Positive clones were isolated from these libraries using appropriate primers. The sequence of the positive clone was determined and found to contain an open reading frame. The nucleotide sequence encoding the human **CARK** protein comprised about 3025 nucleic acids. The protein encoded by this nucleic acid comprised abut 835 (aa)s. A clone containing the rat **CARK** cDNA was also identified. The nucleotide sequence encoding the rat **CARK** protein comprised about 3026 nucleic acids. The protein encoded by this nucleic acid comprised about 835 (aa)s. (158 pages)

L16 ANSWER 2 OF 2 BIOTECHDS COPYRIGHT 2005 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2000-11607 BIOTECHDS
TITLE: New polynucleotide encoding **cardiac-related ankyrin-repeat** protein-kinase, useful for treating disorders such as cardiovascular disorders, e.g. heart failure and cell differentiation disorders, e.g. cancer ;
vector-mediated gene transfer and expression in host cell, antibody, DNA probe and DNA primer
AUTHOR: **Raju J**
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DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2000-431275 [37]
AB A polynucleotide encoding a **cardiac-related ankyrin-repeat** protein-kinase (EC-2.7.1.37) (**CARK**) containing a sequence of 3,025, 2,505, 3,026 or 2,505 bp as defined in the specification, is new. Also claimed are: a nucleic encoding a protein of 835 amino acids; an expression vector; a host cell; a method of producing the protein; an antibody; a method for detecting the presence of the protein; a method for detecting the presence of the polynucleotide using a DNA probe or DNA primer; a kit containing a compound that specifically binds to the protein or polynucleotide; a method for identifying a compound that specifically binds to the protein; a method for modulating the activity of the protein; and a method for identifying a compound which modulates that activity of the protein. The polynucleotides is useful for detecting nucleic acid molecule especially mRNA in a sample, **CARK** encoded by the polynucleotide is useful for treating disorders associated with upregulation or downregulation of cellular proliferation such as disorders concerned with cardiovascular disorders and disorders associated with differentiation of cells such as cancer and sarcoma. (161pp)

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     (FILE 'HOME' ENTERED AT 13:55:08 ON 13 APR 2005)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 13:55:36 ON 13 APR 2005
L1             17 S "CARK"
L2           1949 S "CARDIAC-RELATED"
L3           4025 S ANKYRIN(2W)REPEAT
L4              4 S L2 AND L3
L5              3 DUP REM L4 (1 DUPLICATE REMOVED)
L6             15 DUP REM L1 (2 DUPLICATES REMOVED)
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L7      11583440 S MODULATOR? OR INHIBIT? OR ACTIVAT? OR STIMULAT?
L8          4037 S CARDIAC (2W) RELATED
L9             4 S L8 AND ANKYRIN
L10         2200 S L3 AND L7
L11         1035 S HUMAN AND L10
L12           87 S CARDIAC AND L11
L13           40 DUP REM L12 (47 DUPLICATES REMOVED)
                 E RAJU J/AU
L14          111 S E3
L15            0 S L13 AND L14
L16            2 S (L2 OR L3 OR L1) AND L14
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	L #	Hits	Search Text
1	L1	28	"CARK"
2	L2	0	cardiac adj realted
3	L3	1014	ankyrin
4	L4	61575	cardiac
5	L5	85	l3 same l4
6	L6	58238	kinase$2
7	L7	43	l5 same l6
8	L8	1443395	inhibit$3 or activaT$3 or stimulat$3 or modulat$3
9	L9	38	l7 same l8
10	L10	6	l1 same l8
11	L11	980	RAJU
12	L12	5	(l1 or l9) and l11
13	L13	1	"6660490".pn.
14	L15	1	"6261818".pn.
15	L16	2	l14 l15
16	L14	1	"6500654".pn.

	Issue Date	Pages	Document ID	Title
1	20050317	97	US 20050059147 A1	Human mesenchymal progenitor cell
2	20050106	79	US 20050002917 A1	Regulation of Acheron expression
3	20041209	150	US 20040249127 A1	Intracellular signaling molecules
4	20041202	44	US 20040241148 A1	Dermal micro organs, methods and apparatuses for producing and using the same
5	20041104	138	US 20040219521 A1	Novel nucleic acids and polypeptides
6	20041014	63	US 20040201117 A1	COATED PARTICLES, METHODS OF MAKING AND USING
7	20040701	130	US 20040127406 A1	Methods for in vitro expansion and transdifferentiation of human pancreatic acinar cells into insulin-producing cells
8	20040610	95	US 20040110232 A1	Novel cark protein and nucleic acid molecules and uses therefor
9	20040513	130	US 20040092715 A1	Intracellular signaling molecules
10	20040415	337	US 20040072160 A1	Molecular toxicology modeling
11	20040304	57	US 20040043395 A1	Intracellular signaling molecules
12	20040226	75	US 20040038267 A1	Intracellular signaling molecules
13	20040226	259	US 20040038207 A1	Gene expression in bladder tumors
14	20040219	104	US 20040033504 A1	Novel compounds

	Issue Date	Pages	Document ID	Title
15	20040219	324	US 20040033495 A1	Methods of diagnosis of angiogenesis, compositions and methods of screening for angiogenesis modulators
16	20040212	40	US 20040029151 A1	Molecular genetic profiling of gleason grades 3 and 4/5 prostate cancer
17	20040122	146	US 20040014040 A1	Cardiotoxin molecular toxicology modeling
18	20040108	165	US 20040005560 A1	Novel full-length cDNA
19	20040108	94	US 20040005537 A1	Method of identifying toxic agents using differential gene expression
20	20040101	24	US 20040003424 A1	Transgenic cardiomyocytes with controlled proliferation and differentiation
21	20031218	27	US 20030232340 A1	Nanoporous particle with a retained target
22	20030911	21	US 20030170673 A1	Identification of genes involved in restenosis and in atherosclerosis
23	20030814	55	US 20030152562 A1	Vitro micro-organs, and uses related thereto
24	20030717	62	US 20030134280 A1	Identifying drugs for and diagnosis of benign prostatic hyperplasia using gene expression profiles
25	20030703	56	US 20030124128 A1	Compositions, kits, and methods for identification, assessment, prevention, and therapy of breast cancer

26	20030612	65	US 20030108743 A1	Coated particles, methods of making and using

	Issue Date	Pages	Document ID	Title
27	20030501	78	US 20030082511 A1	Identification of modulatory molecules using inducible promoters
28	20030130	39	US 20030022242 A1	Particles with improved solubilization capacity
29	20020912	94	US 20020127684 A1	Novel cark protein and nucleic acid molecules and uses therefor
30	20020124	57	US 20020009730 A1	Human stress array
31	20050201	39	US 6849611 B2	Implantation of biological pacemaker that is molecularly determined
32	20040622	65	US 6753314 B1	Protein-protein complexes and methods of using same
33	20031209	91	US 6660490 B2	CARK protein and nucleic acid molecules and uses therefor
34	20031028	62	US 6638621 B2	Coated particles, methods of making and using
35	20021231	86	US 6500654 B1	CARK protein and nucleic acid molecules and uses therefor
36	20020101	227	US 6335170 B1	Gene expression in bladder tumors
37	20010717	61	US 6261818 B1	CARK protein and nucleic acid molecules and uses therefor
38	20000530	711	US 6068973 A	Methods for inhibition of membrane fusion-associated events, including influenza virus

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1	20040610	95	US 20040110232 A1	Novel cark protein and nucleic acid molecules and uses therefor
2	20020912	94	US 20020127684 A1	Novel cark protein and nucleic acid molecules and uses therefor
3	20031209	91	US 6660490 B2	CARK protein and nucleic acid molecules and uses therefor
4	20021231	86	US 6500654 B1	CARK protein and nucleic acid molecules and uses therefor
5	20010717	61	US 6261818 B1	CARK protein and nucleic acid molecules and uses therefor
6	19980714	14	US 5780470 A	Melatonergic indanyl piperazines

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1	20040610	95	US 20040110232 A1	Novel cark protein and nucleic acid molecules and uses therefor
2	20020912	94	US 20020127684 A1	Novel cark protein and nucleic acid molecules and uses therefor
3	20031209	91	US 6660490 B2	CARK protein and nucleic acid molecules and uses therefor
4	20021231	86	US 6500654 B1	CARK protein and nucleic acid molecules and uses therefor
5	20010717	61	US 6261818 B1	CARK protein and nucleic acid molecules and uses therefor